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(From a portrait made in 1925)

DISEASES
OF THE SKIN

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ELEVENTH EDITION
WITH 1972 ILLUSTRATIONS

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To

RICHARD LIGHTBURN SUTTON

who dedicated the first eight editions of his book and the ninth and tenth editions of our book to his mother Virginia Robertson Sutton

and

LENA IGEL SUTTON

my mother

IN LOVING MEMORY

and to

SERENA NEEL SUTTON

PREFACE TO ELEVENTH EDITION

Diseases of the Skin has been modernized to accord with medical literature through the date of closing the galley proof. It is comprehensive yet condensed. It aims primarily at usefulness. The illustrations, 1,972 in number are an atlas wherein all ordinary and many extraordinary dermatoses may be identified. The book includes features of a dictionary and an encyclopedia. It is a guide to the maze of what may be found, if one knows where to look, in an extensive medical library It is a systematization of what is known about its subject written from the viewpoint of a practicing physician who is inquisitive

The scholar will find the volume comprehensive I wrote in the preface of our *Handbook of Diseases of the Skin* in 1949 for I have held to the policy of at least mentioning almost everything and have included many thousands of bibliographic entries which enable one to find one s way about in the specialistic literature These may be welcome even to the dermatologist certified as learned, whose memory however disciplined, is unlikely to bear the burden of retaining everything at all times. Reviews of previous books of ours have received earnest deliberation and the constructive criticisms have been adopted where they have not conflicted wi h the necessarily limited size of the book, or with each other or with my desires.

The order of presentation here as in the *Handbook* uses causation as the principal guide to classification, in the hope that it will appear logical to nondermatologists who have tended with justification to think of dermatology as having possessed hitherto to some extent, a viewpoint and language set apart from those of other sciences. I persist in wishing to tie descriptions and concepts of disorders of the skin with general medicine and biology as I wrote in 1938 in the preface of the tenth edition.

The utilization of page space has been painstaking I put half of the words onto two-thirds of the page area available and used 8-point type for material of secondary importance as I did in the *Handbook* To print the book in 10 point only would necessitate publishing it in two volumes. A reader may merit sympathy when he peruses material set in small type I know but reading it is easier than writing it, and printing it, more informative than omitting it. The chapter on diseases due to fungi would in itself make a book of 200 pages. That on malformations and neoplasms would make one of 500 pages with 488 illustrations. I have incorporated more material on the psychosomatic aspects of dermatology than is to be found on the psychosomatic aspects of the whole field of psychiatry in a well known, popular and massive volume on that specialty The 6-point bibliographies total over 5 000 lines of type and present thumbnail abstracts of thousands of articles.

Outstanding are the illustrations. Hermann Pinkus, M D supplied for the *Handbook* a magnificent collection of photomicrographs of normal adult and embryonic cutaneous tissues. I am indebted here, too for his normal material Dr Pinkus prepared for this edition a handsome collection of photomicrographs of abnormal tissues, which are used to illustrate the chapter on Pathology Credit for numerous excellent illustrations is due Drs. J Lamar Calloway O G Costa, Clyde L Cummer Robert N Andrade Emanuel Muskatblit John Belisario and F Ronchese The clinical pictures of Drs. Calloway Costa, Cummer Andrade and Ronchese are scattered throughout the book. Those of

Dr Bellisario are in the section on Carcinoma Those of Dr Muskatblit, showing fungi and diseases caused by them, are of unusual excellence as are also those so generously given to me for previous editions by Drs. George M Lewis and Mary Hopper The privilege of taking what I desired from *Oral Pathology* by Kurt Thoma and from *Skin Manifestations of Internal Disorders* by Kurt Wiener deserves especial acknowledgment. To Dr Gustav Riehl I am indebted for many fine illustrations of cutaneous tuberculosis, to Dr S William Becker for a group showing the histology of nevi and melanomas, and to Drs. Duncan Loth and J J Zoon for groups showing keratoacanthoma.

The bibliography as a whole consists of that which is incorporated in the text plus that which is postscripted to the particular section. This latter material contains what I did not fit into the text yet desired to mention. To many such references I have added a word or two identifying them refreshing the memory of one who has read them before or giving some idea of the content to one who has not.

In judging the ideas that are quoted so profusely in the text, one should note the dates of the references I was aware of them.

Documentation can be accomplished in only a few ways. Superscript numbers and corresponding terminal references are not practicable. Footnotes are hopelessly confining when one intends to re-edit a book, for classifications change in fifty years. Finally why insert (Smith, 1951) and oblige the reader to look to the end of the topic for the bibliographic reference when one can insert (Smith Lancet 2 1020 1951) and have done with it? I asked many friends for advice about styles of documentation and learned that two-thirds of them preferred mine and four fifths of them considered mine either preferable or acceptable

Credit within the text, the bibliographies, and the titles of illustrations is everywhere carefully given. For that too which is original, the source is indicated. My opinions are nowhere hard to find. I remember with gratitude a review by a man who approved of my expression of personal opinions that man will like this book. I claim some originality in paragraphs to be found hereinafter on several topics the treatment of contact dermatitis the interpretation and treatment of acne the histologic and clinical understanding of early epidermoid carcinoma the interpretation of autoeczematization and its relation to hypoproteinemia what to do about chronic dermatitis of undetermined etiology especially when it affects the hands a certain hyperkeratotic form of volar dermatitis the treatment of prurigo nodularis and of calcinosis universalis *Microsporum canis* infection of the finger tips; *Gaffkya tetragena* infections of the skin what I have chosen to call Summertime pityriasis of the elbows and knees summer acne of the extremities and apocrine cysts of the scalp which I have not seen described elsewhere.

Dr Charles R Rein wrote the section on Serology of Syphilis, as he did for the tenth edition and the *Handbook*

Dr F Stanley Morest read the section on Peripheral Vascular Disorders. The improvements he recommended attest to his extensive and effectual knowledge of this subject

The galley proof on Leprosy was read by Rolla R Wolcott, M.D., Medical Director U S Public Health Service Hospital, Carville, Louisiana, and the material was conformed with his invaluable criticisms. I am grateful to Hermann Pinkus, M D., further for he graciously pointed to certain corrections desirable in the page proof of the chapter on Anatomy to Walter C. Lobitz, Jr M D., who did this for the chapter on Physiology and the section on Diseases of the Sweat Glands, and to Sloan Wilson, M.D., who did it for the section on Purpura What imperfections remain are not the fault of these kind friends.

Gilbert E Ryder M D for whom I am presently preceptor under the American Board of Dermatology and Syphilology read all of the page proof

with me There is not a "dilatation" in the book other than this one, not a "therapeutic armamentarium" We corrected an occasional misspelling in a *direct quotation in order to avoid an uncharitable* [sic]

The index is pointed out as a source of a variety of information and guidance, especially under such titles as "Disease" "Prescription," "Syndrome" and "Test"

Abbreviations of references are listed on p xix, ff preceding the text

Many have asked me how such a book as this is made One obviously depends on the publications of others, to which one's own observations and opinions are added. Among the requisites are time experience in the practice of medicine (to which I have by now devoted some twenty five years) and a generous measure of stubbornness. Of writing a book Winston Churchill said, "To begin with, it is a toy and an amusement. Then it becomes a mistress, then a master, then it becomes a tyrant. Finally when you are reconciled to your servitude, you kill the monster"

I have worked during morning hours, protected from every kind of interruption by teammates, who have occasionally been obliged to tax their consciences in defending me from people who itch. During 1953 a partnership with Norman D Asel M.D., was established. To our comfortable and satisfying relationship I am indebted for many hours that could have been granted me in no other way I am grateful for the cheerful and efficient cooperation of Miss Margaret Egy my patient secretary skilled not only in orthography and syntax but also in getting along with a moody man and of Mrs. Betty Standke Miss Mildred Young Mrs. Corinne Gallup, Mrs. Margaret Lynch, and Mr Robert Sauvan.

Systematic reading is required. For years I have abstracted onto 3 x 5 file cards everything appertaining to dermatology that crossed my desk. These are cast alphabetically by subject matter In abstracting I record that which appears to add to my own knowledge. Most articles contain, of what I want less than enough to crowd one side of a file card. The content of an exceptional essay may oblige me to use several sentences. One that I could not condense much, for example was that of Bedford Shelmire (J 113 1085 1939) on dermatitis due to plants, of which I quoted whole paragraphs (p 154) Some articles condense to nothing at all.

My descriptions of a disease frequently take the form of a reference to the original recognition of the entity a statement of what may be called its average manifestations, and then several case references suggesting range variability or extremes of its potentialities. The mention of rare odd or curious instances helps, I imagine in formulating a concept of the condition. Also to me these are interesting

In revising a description of a disease I put together the pertinent group of file cards, some of which are cross references, like fragments of a mosaic. Sometimes an article is quoted with respect to only a fraction of its content, particularly if it covers a certain facet of the subject nicely and I cite other articles appropriate to document other facets.

Here and there I quote a statement or hypothesis that is patently absurd although not to its originator I have done this to dispel ennui and to exemplify some of the contemporary "thinking" that is not critical (see Asher BMJ 2 460 1954) Yet to me there is apparent in what I have written some mellowing with maturity as evidenced by a recently acquired lack of conviction that certain opinions of others are wrong or that opinions of mine are right. Credit has evolved into credibility certitude into wonder faith into hope Thus where I have expressed my views, I may have antagonized fewer individuals in this edition than formerly and in places I have actually avoided disputation.

Pertinent is a quotation you will enjoy from an obscure source my father and I happened upon. John Smith, M.D E., Coll. Med. Lond. Cand., published *King Solomon's Portraiture of Old Age Wherein Is Contained a Sacred*

Anatomy Both of Soul and Body in 1666 His Epistle to the Reader ' in contrast with what was then customary, was not devoted to flattery of a patron John Smith whatever might have been his now quaint ideas on sacred anatomy of soul and body was a man one would like to know and his preface, cold from his pen these 290 years, pleases me (I wish I could tell him so) Whosoever thou are into whose hands this Paraphrase may fall know that the Author of it is not near enough any Nobleman to put it into his hands, nor hath he face enough to call at a distance, but could he do both, yet know also he would do neither for he desireth not that anything either of others or of his own should be patronized beyond its own native worth, And is himself willing that all the shame that is due to the ill managing of this good Subject should return upon his own pate "

Those to whom Senior can be only a tradition may wish to become acquainted with the man who initiated this book in 1916 and put it through eight editions single handed by 1931 My father was friendly communicative buoyant desirous of approval. When he became famous he enjoyed it immensely He was the antithesis of colorless, being uninhibited in expressing vivid views. His contemporaries do not forget him he did not bore them. Fishing and hunting were coequal with medicine in his enthusiasm and he covered the earth in his travels. Vast numbers of persons from all walks of life adored him Few have filled the hours of a lifetime so full. Obituaries were written by *Harold N Cole (ADS 66 424 1952) John Belisario (Austral* JDermat 1 263 1953) and myself in the Yearbook (1951 1952) of the Royal Society of Edinburgh.

My father retired in 1940 to devote himself to the hunting and fishing he so dearly loved. His health did not long remain good. While new editions had been his almost biennial habit, the eleventh remained only an ambition for a number of years. The necessity for revising our *Introduction to Dermatology* in 1941 and my entry into military service not long thereafter caused delay By 1949 I had prepared our *Handbook* for publication, after which I again gave thought to tackling the Big Red Book. Senior s death in May of 1952 made the task seem impossible He had the ability to make hard work easy and to revivify when energy flagged. His decisions were instant and generally right, and his capacity for turning out work commanded the respect even the awe of those who knew him.

In the preface of the first edition of *Diseases of the Skin* published in 1916 with 916 pages and 701 illustrations, my father said The present volume is the outgrowth of several years of study along this particular line and is an attempt to present the entire subject of dermatology in a comprehensive and at the same time concise manner A treatise covering so broad a field cannot well be based entirely on the personal knowledge and observations of any single individual For this reason I have not hesitated to draw from the publications of other writers selecting the material which I considered most appropriate Every effort has been made to properly credit the ideas thus secured. The majority of the therapeutic measures recommended are those which I have found useful and practicable in my own practice

The second edition appeared in 1917 containing 1021 pages and 841 illustrations. The preface read, The demand for a second edition at this time has given me opportunity to supply supplemental matter in a few instances, as well as to cover the important literature of the year 1916 and to eliminate a number of typographic and other minor errors. I am deeply grateful to my friends and colleagues for the kind and generous reception accorded the first edition

The third edition with 1084 pages and 921 illustrations, appeared in 1919 While the war has had a deterrent effect upon the study of cutaneous medicine in general it has added to our knowledge of the successful management of a few disorders, notably those due to animal parasites and has

developed a few new affections, such as occupation and traumatic dermatoses due to tetryl dichlorethylsulphide and similar chemical irritants. The gravity of syphilis as a social disease is becoming more evident each year a fact to which attention has been called by the splendid contributions of William Allen Pusey John H. Stokes, Loyd Thompson, H. H. Hazen and other authorities. The important part played by focal infections in the causation of disorders of the skin is at last becoming generally recognized I am indebted to many colleagues for valued suggestions and advice and particularly to my friend, Dr Charles J White of Boston whose encouragement and example have been constant sources of inspiration during my entire dermatological career '

The fourth edition was published in 1921 with 1132 pages and 980 illustrations. The clinical and serological study of syphilis continues to hold the attention of a large and able body of investigators, and the general public is at last beginning to appreciate the widespread prevalence and disastrous consequences of this malady The researches of Ormsby and Mitchell Charles J White Wende and Wilkinson and others, on epidermophyton infection and its etiologic relationship to certain chronic inflammatory disorders of the skin, have served to call attention to an important field which has hitherto been sadly neglected in this country

The fifth edition, in 1923, contained 1214 pages and 1080 illustrations. To one who has had a watchful finger on the pulse of dermatological literature for a decade and a half the output for the past two years is as promising as it has been prolific. I am indebted to my son, Richard L. Sutton, Jr., for many of the photomicrographs.

The sixth edition, in 1926 contained 1303 pages and 1158 illustrations. Additional light is constantly being thrown on a number of cutaneous disorders, and while our therapeutic advances have not kept pace with the information gained along other lines, we at least are in position to combat the various mycotic disorders far more intelligently if not more successfully than we were a decade ago

The seventh edition appeared in 1928 with 1394 pages and 1248 illustrations. Several recently discovered diseases have been introduced, the descriptions of some of the older ones rewritt_n, and the importance of others, such as certain of the occupational dermatoses and those related to allergy emphasized. An attempt has been made to discuss intelligibly the latest developments in cutaneous therapy and to recommend those agents known to be reliable and practicable. In order to economize space a considerable number of valuable references have had to be confined wholly to footnotes otherwise the volume would soon become so bulky and unwieldy as to seriously impair its usefulness.

The eighth edition was published in 1931 with 1352 pages and 1301 illustrations. Modern dermatological literature appears to grow by leaps and bounds. It is essential that each new edition contain an easily accessible and complete record of all the authoritative reports that have appeared in the interval This I have endeavored to do to the best of my ability, but even the most skilled of phraseological artists will experience difficulty in condensing and crystallizing the wisdom of a three thousand word masterpiece into the space of one or two brief sentences and I must acknowledge that I am no literary Cellini. Scanning the completed task, no one realizes better than I how incompletely it fulfills the ideal.'

The ninth edition, the first of Sutton and Sutton coauthorship was published in 193_ with 1433 pages and 1321 illustrations. Twenty years ago when I began collecting material for the first edition of this work, Senior wrote little did I suspect that it would ever grow into the present ponderous volume. Had I done so it is very probable that I should have tried to content myself with labors that demanded far less time and effort. A book of this sort is like a child the author an anxious and doting parent.

The tenth edition, a three-year labor of rewriting appeared in 1939 with 1549 pages and 1473 illustrations. With emendations it was reprinted in 1942 and again in 1943 We imagined that we had systematized the progressively increasing difficulty of reflecting current dermatology in such a fashion that future editions would be relatively easy to prepare I wrote the preface that time In view of the favorable reception accorded the etiologic classification in the 1937 edition of our *Introduction to Dermatology* and the tendency nowadays to inquire What is going on? rather than What name is applicable to this manifestation? the material has been arranged in a fashion radically different from that in the ninth edition. Descriptions of all significant entities, syndromes and concepts, and of many exotic unusual and even exceptional dermatoses have been incorporated. Emphasis is laid, however on the purpose of practical medicine which is to cure the ordinary patient of his ordinary complaints by scientific or by pragmatic means.

Quotations from prefaces of the past indicate that the endeavor to reflect contemporary medical thinking and practice involves a variety of problems. They are problems that become more and more challenging as one measures the capacity of a human being against the quantity of dermatologic science (and fiction) that appears in print

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CONTENTS

ABBREVIATIONS OF BIBLIOGRAPHIC REFERENCES

A	Archives (of)
abs	Abstracted in
ActaD-V	Acta dermato-venereologica
ActaMScand	Acta medica scandinavica
AD	A.M.A. Archives of Dermatology continuation after 1954 of A.M.A. Archives of Dermatology and Syphilology
ADS	A.M.A. Archives of Dermatology and Syphilology
AfDuS	Archiv für Dermatologie und Syphilis
AfpathAnat	Virchow's Archiv für pathologische Anatomie und Physiologie und für klinische Medizin
AIndustH g	A.M.A. Archives of Industrial Hygiene and Occupational Medicine
AIntM	A.M.A. Archives of Internal Medicine
AmHeartJ	American Heart Journal
AmJAnat	American Journal of Anatomy
AmJCa c	American Journal of Cancer
AmJClinPath	American Journal of Clinical Pathology
AmJDigDis	American Journal of Digestive Diseases
AmJMed	American Journal of Medicine
AmJMedSci	American Journal of the Medical Sciences
AmJObGyn	American Journal of Obstetrics and Gynecology
AmJOphth	American Journal of Ophthalmology
AmJPath	American Journal of Pathology
AmJPhysiol	American Journal of Physiology
AmJPsych	American Journal of Psychiatry
AmJPubH	American Journal of Public Health a d the Nation s Health
AmJRoentg	American Journal of Roentgenology Radium Therapy and Nuclear Medicine
AmJSurg	American Journal of Surgery
AmJSyph	American Journal of Syphilis, Gonorrhea and Venereal Diseases
AmJTropM	American Journal of Tropical Medicine
AmMed	American Medicine
AmRe T berc	American Review of Tuberculosis
AnatRec	Anatomical Record, Wistar Institute
Angiol	Angiology The Journal of Vascular Diseases
Ann	Annals
AnnAllergy	Annals of Allergy
AnndeD	Annales de dermatologie et de syphiligraphie
AnnIntM	Annals of Internal Medicine
AnnOtol	Annals of Otology Rhinology and Laryngology
AnnSurg	Annals of Surgery
AnnTropM	Annals of Tropical Medicine and Parasitology
AnnWestM&S	Annals of Western Medicine and Surgery
ArchArgentD	Archives argentinos de dermatologia
ArchBelgD	Archives belges de dermatologi et de syphilographie
ArchDisChild	Archi es of Disease in Childhood
ArchIndustHyg	A.M.A. Archives of Industrial Hygiene and Occupati nal Medicine
ArchItalD	Archivio itali no di dermatologia, sifilografia, e venereologia
ArchNeurol	A.M.A. Archives of Neurology and Psychiatry
ArchOphth	A.M.A Archives of Ophthalmology
ArchOtol	A.M.A. Archives of Otolaryngology
ArchPath	A.M.A. Archives of Pathology
ArchPediat	Archives of Pediatrics
ArchPhysMed	Archives of Physical Medicine
ArchSurg	A.M.A. Archi es of Surgery
ArizM	Arizona Medicine
AustralJD	Australian Journal of Dermatology
BeitrklinChi	Beiträge zu klinischen Chirurgie
BiochemJ	Biochemical Journal, Cambridge
BiolRev	Biological Reviews
BJD	British Journal of Dermatology and Syphilis
BJVD	British Journal of Venereal Diseases
BMJ	British Medical Journal

BritHeartJ	British Heart Journal
BritJCanc	British Journal of Cancer
BritJExpPath	British Journal of Experimental Pathology
BritJIndustM	British Journal of Industrial Medicine
BritJOphth	British Journal of Ophthalmology
BritJPhysMed	British Journal of Physical Medicine and Industrial Hygiene
BritJRadiol	British Journal of Radiology
BritJSurg	British Journal of Surgery
BritMedBull	British Medical Bulletin
BsocfrançD	Bulletin de la société française de dermatologie et de syphiligraphie
Bull	Bulletin
BullJHH	Bulletin of the Johns Hopki s Hospital
BullmémSocMéd	Bulletins et mémoires de la Société médicale des Hôpitaux de Paris
BullNYAM	Bulletin of the New York Academy of Medicine
BullUSAMD	Bulletin of the United States Army Medical Department
CalifM	California Medicine
CalifWM	California and Western Medicine
CanadMAJ	Canadian Medical Association Journal
CanadPHJ	Canadian Journal of Public Health
CancRes	Cancer Research
ChinMJ	Chinese Medical Journal
Circ	Circulation. The Journal of the American Heart Association
ClevClinQ	Cleveland Clinic Quarterly
Clin	Clinics
ClinSci	Clinical Science Incorporating Heart
ConnMJ	Connecticut State Medical Journal
CurMDig	Current Medical Digest
DmedWchn	Deutsche medizinische Wochenschrift
DWchn	Dermatologische Wochenschrift
DZtschr	Dermatologische Zeitschrift
EAfrMJ	The East African Medical Journal
EdinMJ	Edinburgh Medical Journal
Edit	Editorial
Endocr	Endocrinology
FlaMAJ	Journal of the Florida Medical Associ tion
Geriat	Geriatrics
GiorItalD	Giornale italiano di dermatologia e sifilogia
HandbHuG	Handbuch der Haut und Geschlechtskrankheiten Springer
IllMJ	Illinois Medical Journal
IndJMRes	Indian Journal of Medical Research
IndMGaz	Indian Medical Gazette
Ind tM	Industrial Medicine and Surgery
InternatCl n	International Clinics
Int rnatJLep	International Journal of Leprosy
IrishJMSc	Irish Journal of Medical Science
J	Journal of the American Medical Association
JAllergy	Journal of Allergy
JAmDentA	Journal of the American Dental Association
JAnat	Journal of Anatomy
JapJD	Japanese Journal of Dermatology
JB&JS rg	Journal of Bone and Joint Surge y
JBact	Journal of Bacteriology
JB och	Journal of Biochemistry J panese Biochemical Society Tokyo
JB olChem	Journal of Biological Chemistry
JCl E dor	Journal of Clinical Endocrinology and Metabolism
JCl I	Journal of Clinical Investigation
JClinP th	Journal of Clinical Pathology
JC tD	Journal of Cutaneous Diseases
JDe tRes	Journal of Dental Research
JExpe B ol	Journal of Experimental Biology
JExpe M	Jo rnal of Experimental Medicine
JFlaM A	Journal f the Florida Medical Association
JGero t l	Journ l of Gerontology
JHyg	Journal f H giene
JID	J urnal of In estigative Dermatology
JImmu ol	J urnal of Immunology
JIndianaMA	J urnal of the Indiana State Medical Association
JIndustHyg	Journ l of I dustrial Hygiene and Toxicology

JInfectD	Journal of Infectious Diseases
JIowaMS	Journal of the Iowa State Medical Society
JKansMS	Journal of Kansas Medical Society
JLabClinM	Journal of Laboratory and Clinical Medicine
J Lancet	Journal Lancet
JLaryngol	Journal of Laryngology and Otology
JMAGa	Journal of Medical Association of Georgia
JMedRes	Journal of Medical Research
JMichSMS	Journal of the Michigan State Medical Society
JMoMA	Journal of the Missouri State Medical Association
JMSocNJ	Journal of the Medical Society of New Jersey
JNatlCaInst	Journal of the National Cancer Institute
JNervMentDis	Journal of Nervous and Mental Disease
JNeuropath	Journal of Neuropathology and Experimental Neurology
JObGyn	Journal of Obstetrics and Gynaecology of the British Empire
JOklaMA	Journal of Oklahoma State Medical Association
JPathBact	Journal of Pathology and Bacteriology
JPediat	Journal of Pediatrics
JPharm	Journal of Pharmacy and Pharmacology
JPharmExpTher	Journal of Pharmacology and Experimental Therapeutics
JPhilipMA	Journal of the Philippine Medical Association
JPhysiol	Journal of Physiology
JRoyAMC	Journal of the Royal Army Medical Corps
JTennMA	Journal of the Tennessee State Medical Association
JThoracicSurg	Journal of Thoracic Surgery
JTropM	Journal of Tropical Medicine and Hygiene
JUrol	Journal of Urology
JVDI	Journal of Venereal Disease Information (merged with Public Health Reports)
KlinWschr	Klinische Wochenschrift
KyMJ	Kentucky Medical Journal
Laryng	Laryngoscope
LyonChir	Lyon chirurgie l, Bulletin officiel de la Société de chirurgie de Lyon
Med	Medicine Analytical Reviews of General Medicine Neurology and Pediatrics
MedAnnDC	Medical Annals of the District of Columbia
MedClinNoAm	Medical Clinics of North America
MedMex	Medicina Revista Mexicana
MilSurg	Military Surgeon
MinnM	Minnesota Medicine
MJ&R	Medical Journal and Record
MJAustral	Medical Journal of Australia
MoMed	Missouri Medicine Journal of the Missouri State Medical Association continuation of JMoMA
MonatshprakD	Monatshefte für praktische dermatologie
MP&Circ	Medical Press and Circular
MRec	Medical Record
MTimes	Medical Times
NCarolMJ	North Carolina Medical Journal
NebrMJ	Nebraska State Medical Journal
NederlTijdschrGeneesk	Nederlandsch tijdschrift voor geneeskund
NOrlM&SJ	New Orleans Medical and Surgical Journal
NoWMed	Northwest Medicine
NYSJM	New York State Journal of Medicine
ObGyn	Obstetrics and Gynecology Journal of the American Academy of Obstetrics and Gynecology
OhioMJ	Ohio State Medical Journal
PaMJ	Pennsylvania Medical Journal
Parasit	Parasitology
PHRpts	Public Health Reports
PhysiolRev	Physiological Reviews
PIMChi	Proceedings of the Institute of Medicine of Chicago
Pract	Practitioner
PresseM	La presse médicale
ProcRoySocM	Proceedings of the Royal Society of Medicine
PSExperBiol	Proceedings of the Society for Experimental Biology and Medicine
PSMMC	Proceedings of the Staff Meetings of the Mayo Clinic
PsychosomM	Psychosomatic Medicine

QMN	Queries and Minor Notes, in the Journal of the American Medical Association
QuartJMed	Quarterly Journal of Medicine
Radiol	Radiology
RevargentD	Revista argentina de dermatosifilologia
RevMMex	Revista de medicina y ciencias afines
RhodeIsMJ	*Rhode Island Medical Journal*
RifMed	La riforma medica
RockyMtMJ	Rocky Mountain Medical Journal
SchweizMWchn	Schweizerische medizinische Wochenschrift
Sci	Science
SGO	Surgery, Gynecology and Obstetrics
SoAfrMJ	South African Medical Journal
SouthMJ	Southern Medical Journal
SouthM&S	Southern Medicine and Surgery
SouthSurg	The Southern Surgeon
SouthwestM	Southwestern Medicine
Surg	Surgery
SurgClinNoAm	Surgical Clinics of North America
TexasSJM	Texas State Journal of Medicine
Tran AssnAmPhys	Transactions of the Association of American Physicians
UCutRev	Urological and Cutaneous Review
USAFMJ	United States Armed Forces Medical Journal
USNMBull	United States Naval Medical Bulletin
VaMMonth	Virginia Medical Monthly
VDI	Journal of Venereal Disease Information
WarM	War Medicine
WDTBM	War Department Technical Bulletin, Medicine, Washington, D. C.
WestJSOG	The Western Journal of Surgery, Obstetrics and Gynecology
WienMWchn	Wiener Medizinische Wochenschrift
WiscMJ	Wisconsin Medical Journal
WVaMJ	West Virginia Medical Journal
YaleJBiol	Yale Journal of Biology and Medicine
YBD	Year Book of Dermatology and Syphilology, Year Book Publishers
ZtschrBakt	Zeitschrift für Bakteriologie
ZtschrHyg	Zeitschrift für Hygiene und Infektionskrankheiten
Ztsch Kinderh	Zeitschrift fur Kinderheilkunde
ZtschrPath	*Frankfurter Zeitschrift fur Pathologie*

DISEASES

OF THE SKIN

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ANATOMY

The skin is a soft, flexible membranous covering which completely invests the body and is continuous at the natural orifices with the mucous membranes. It consists of (1) a connective tissue frame incorporating blood vessels, lymph vessels and nerves, collectively comprising the dermis, and (2) an epithelial covering the epidermis. Dermis is that which becomes leather when skin is tanned Epidermis is that which forms the cap of a blister

The skin ranges considerably in thickness and consistency on various parts of the body It is the largest organ of the body weighing three times as much as the liver It serves principally in protection, heat regulation sensation and secretion. It is attached loosely or firmly to underlying structures so as to resemble a closely fitting elastic garment. Its area averages 16,000 to 18,500 cm.[2] and its weight 3 000 to 3,500 gm. (Leider JID 2 187 1949) The weight of the epidermis is approximately 225 gm. The specific gravity of the whole glabrous skin is 1.1, while for hair and nail the figure is about 1 3 (Leider and Buncke ADS 69 563 1954)

Superficially the skin is marked by tiny wrinkles and furrows. Underlying glands communicate with the surface through pores. On the palms and soles occur parallel ridges corresponding to rows of underlying dermal papillae.

Subcutaneous tissue is composed mainly of adipose lobules. It unites a regular surface with the deep fascia covering muscle and bone, and forms a resilient base for the overlying skin. Lobules of adipose tissue are latticed by an areolar fibrous network which supports blood vessels and nerve trunks. Thickness of the adipose layer was investigated by Stuart and Sobel (JPed 28 637 1946) Fat is an important but ill understood special tissue and storehouse (Wells PIMChi 13 26 1940)

Lines of cleavage result from the disposition of collagenous bundles under the influence of tension. In general, they parallel the natural creases and the direction of the hair roots (Cox BJS 29 234, 1941)

Color is determined by the pigment in the upper layers, by the blood of the capillaries in the dermis and by carotene It may be altered by vasoconstriction, vasodilation, cyanosis, methemoglobinemia, sulfhemoglobinemia, acrocyanosis, local asphyxia, dehydration and edema, as well as by pigmentation of external or internal origin, and by the thickness of the epidermal covering

Epidermis.—This ectodermal vestment consists of cornifying stratified squamous epithelium It is apposed to the papillated surface of the underlying specialized mesodermal structure the corium, or dermis. The basal membrane is the adhesive substance conjoining epidermis and dermis and behaves like a collagen gel, for separation of epidermis from dermis is effected by acids and bases at those hydrogen ion concentrations which cause swelling of gelatin (Felsher JInvD 8 35 1947) Agents which swell these hydrophilic colloids, including NaSCN and NaI decrease their cohesiveness, a fact which may explain their influence on dermatitis herpetiformis. Shrinking agents include Na_2SO_4 and Na citrate in 2N concentration. Karyokinetic division furnishes the layers from within outward. Mitoses occur twice as frequently in the night as during the day (Broders and Dublin PSMMC 14 423 1939) and epidermis of glabrous skin renews itself continuously from within outward in about 7 days, corneous scales flaking off inconspicuously under normal conditions

The ultimate derivation of superficial epidermal cells is, of course, from the basal layer and from below outward there may be described (1) the

stratum mucosum (2) the stratum granulosum, (3) the stratum lucidum and (4) the stratum corneum. The alterations in appearance of the cells as they are pushed outward are not evidence that they are intrinsically different. A basal cell its daughter cells in the mucosal layer and the derived cells in the horny layer are all of the same strain and manifest changes due to environ ment rather than to differentiation.

The deep layer consists of palisaded basal cells elongated perpendicularly to the surface The superficial ones become polygonal and flattened. These comprise the prickle-cell layer or stratum mucosum Its cells are soft and mucoid, nucleated and rich in cytoplasm their surfaces are covered with short protoplasmic spines, which give individual cells a cocklebur appearance. The structure of epithelial cells at high magnification was studied by Gray et al (JID 10 449 1952) The intercellular bridges may be in fact cytoplasmic tubes connecting the cytoplasm of adjoining cells in a syncytium (Laden et al. JID 19 211 1952 see Allen The Skin, Mosby 1954 p 5 ff.)



Fig. 1 —Normal skin from trunk (Dr H Pinkus.)

Mitoses are not limited in occurrence to the basal layer (Pillemer et al.: JExperM 70: 387 1939) In fact most mitotic figures are seen i the stratum spinosum, in fresh human scalp material (Thuringer: JID 2: 313, 1939) More mitoses take place during the night than during the day according to Cooper and Schiff (ProcSocExperBiol 39: 323, 1938) In volar epidermis mitoses are seen especially during rest and during and after stimulation (Thuringer) peak reproductive rates being reached independently in the basal nd spi ous l yers, respectively one and two hours after stimul tion. Maximal acti ity in preputial tissue was found at from 9 to 10 P.M. and minimal at from 5 to 10 A.M. by Cooper (JID 2 289 1939) The night rate is about twice the day rate (Broders and Dublin: PSMMC 14 423, 1939) The colchicine method of demonstrating mitoses revealed ac tivity in the entire Malpighian layer, according to Uehlinger et al. (JID 4: 331 1941) Mitos s eq ires about half an hour Hoffman (APath 47 3 , 1949) estimated, calculating that while one basal cell undergoes division some eight cells are being produced in the spinou laye He calculated that a basal cell in scalp tissue may spend about 3100 hours as such a prickle cell spe ds 2900 hours as such, d a granular cell about 1900 hours as such. When epidermis of glabrou kin is removed from patient by means of the actual cautery n w epithelium covers the defect in from 5 to 7 days. Thi is also the time re qu red fo the granula layer sta ned by silve nitrat to be shed and replaced. Unde normal cond tions the loss of corneou scales is entirely inconspicuous. The quantity of ep lermal material which is continuou ly bei g produced is notabl when, fo ample, an ocel lress g l t th normal loss.

The outermost cells of the prickle layer are differentiated, forming the stratum granulosum. They lie flattened parallel with the surface and con tain, in addition to degenerating nuclei coarse basophilic granules of kerato-hyaline which is a precursor of the horny substance of the corneum There is abrupt transformation from the stratum granulosum to a thin transparent



Fig. 2.—Normal skin from digit, showing corneum and eccrine sweat glands. (Dr H. Pinkus.)



Fig. 3.—Skin of digit, showing normal corneum, epidermis and papillary portion of dermis. Sweat duct in epidermis is seen centrally. (Dr H. Pinkus.)



Fig. 4.—Epidermis, showing keratinization, granular layer and corneum. (Dr H. Pinkus.)

layer the stratum lucidum. *Prominent* in volar skin and absent in many regions, *this consists of clear, flat cells containing* droplets of eleidin, but nuclei and cell membranes are inconspicuous in ordinary preparations. Eleidin probably is intermediate chemically between keratohyalin and keratin. The outermost layer the stratum corneum, is composed of flat imbricated keratinized cells of which the superficial ones are horny scales (Ludford QJMicroscSc 66 27 1924) Keratin, the main constituent of the corneum is relatively resistant to acids, but less so to alkalies.

Molecular aspects of cornification were investigated, using electron microscopy, by Meirowsky and Freeman (JID 21: 83 1953) who found reasons to believe that keratin is a growing substance, not inert. Electron microscope studies of epidermal fibers show the intercellular bridges clearly and these appear to terminate at the cell boundaries, reported Adolph et al. (Sci 113: 685, 1951) The precipitated cytoplasm exhibits a fine felt work of fibers which are different in size from the intracellular fibers and seem not related to the intercellular bridges. Electron microscopy of the skin was also studied by Pease (AmJAnat 89: 469 1951) and Laden et al. (AD 1 19 1956)

Bizzozero s nodules are nodular thickenings of the intercellular bridges. Favre et al. (AnndeD 6 537 1947) noted that they are stained by Heidenhain's iron hematoxylin, although the bridges themselves, the cytoplasm and the nucleus remain colorless with this stain. The nodule is not always in the center of the bridge. It may be ovoid or fusiform. Where keratohyalin granules are voluminous the nodules are not seen but can be detected more superficially in the horny layer as a wreathlike arrangement in the outer dense layers. They do not occur in epithelium of mucous membranes unless there is definite keratinization. Favre et al. concluded that the structures are intercellular epidermal corpuscles, autonomous and not representative of fusion points of intercellular spines, possibly related to the chondriomes of the protoplasm for they take the mitochondria stain. Mitochondria were studied by Regaud and Favre (AnndeD 10: 241, 1950), who described them *as long coarse wavy filaments parallel to the cell surfaces of the basal* and prickle cells, characteristically spiral, found in epidermis of volar skin, not in the granular layer They disappear in psoriasis and in various other abnormalities.

Histochemical studies of the intercellular material were made by Dupré (AnndeD 80 490 1953 abs ABD 1954, p. 338) McManus stain showed Bizzozero's nodules rose colored, nodular o fusiform, often with a median bulge. In the stratum granulosum they formed a continuous moniliform line In the corneum they formed an irregular framework for the keratinized cells. They were not found between cells of the basal layer They stained deep black with Sudan black B. It appe red that the intercellular substance a complex lipid-glucoid protein, forms a histochemical unit at the dermo-epidermal junction and more superficially, and that the semiliquid, McManus-positive portion solidifies into nodules in the intercellular bridges.

As Pinkus (JID 16 383, 1951) has emphasized there is only one race of epidermal cells from the basal to the outermost layer The cells of this one race are called by different names depending on their position in the mattress like *three dimensional epidermis, and on their state of differentiation.* The prickle cells are usually larger than the basal cells, both in nucleus and body and stain lighter The nucleus is round or oval with a thick nuclear membrane and with usually one or two large collections of chromatin. The cytoplasm is divided into two zones, a small inner zone called endoplasm by Studnicka containing a relatively small number of chondriosomes and the Golgi net and outside this the main part of the cell body the exoplasm tougher in consistency and containing the tonofibrils. Tonofibrils are protoplasmic differentiations barely visible in routine preparations but capable of being stained by special methods. They are wiry fibrils which traverse the cells and form a basketlike net around the nucleus. They extend from one cell to another through the intercellular bridges.

Pinkus has observed that both basal and prickle cells are capable of movement if a small fragment of skin is isolated under favorable conditions. It is a mass movement comparable with the flow of lava so that the available material covers a larger area. During this migration the cells change their shape and give up their system of tonofibrils and intercellular bridges, so that the cells come to touch each other with broad surfaces. Tonofibrils do not re-form in isolated epidermal cells, but if the culture stops growing and establishes an equilibrium tonofibrils form again. When cells separate from each other the t n fibrils pass through remaining spots of contact but prickles, intercellular bridges and tonofibrils are not identical A differential staining

technic for mitochondria, tonofibrils (including Herxheimer s spirals) and desmosomes in skin sections was given by Pinkus and Steele (JID 22 367 1954)

Keratohyalin occurs in only one or two layers of normal skin, except in those regions with a thick horny layer the palms and soles, where multiple layers of granular cells are to be found.

At follicular orifices the cells are arranged in a circular manner supplying a lining for the ducts Ducts of sweat glands are separate from other epidermal cells, though resembling them. Between the deep cells of the epidermis are branched dendritic pigment-containing cells. Clear cells balloon like and perhaps of neural function also occur among the cells of the basal layer see melanoblasts (p 787)

Separation of the Epidermis.—Epidermis may be lifted off the dermis by blunt dissection after the skin has been soaked for about 30 minutes at 20 C, in isosmotic ammonia, but the deep portions of hair and gland structures remain in the dermis (Baumberger et al: JNatlCaInst 2: 413, 1942) Dilute acetic acid may be used for this purpose, and Blank and Miller (JInvD 15: 9 1950) used a suction technic. When transparent adhesive tape is applied to the skin a single layer of horny cells adheres to it, a d repeated applications show that the forearm corneum is from 10 to 40 cell layers in thickness (Pinkus: JInvD 16: 383, 1951)

The loss of keratin by stripping apparently served as a stimulus of epidermal proliferation stated Pinkus (JID 19: 431 1952) who studied quantitatively the regenerative process. Hypertrophy of the cells and their mitosis were more pronounced in the basal layer than peripherally

Maceration was used to separate the epidermis from the dermis in both normal and abnormal conditions as illustrated by Horstmann (AfDuS 194 104, 1952) Chloropre e dimers, allyl laurate or iodoacetic acid can be used to effect the separations (Flesch et al.: JID 18: 187 1952)

If a thin strip of skin is stretched to its limit and anchored with thumbtack the epidermis can be grasped with forceps and teased off in a continuous sheet (Van Scott: JID 18: 377, 1952) *The adhesiveness of epidermal cells varies inversely with the temperature* (Zeldman: Sc 109 596 1949)

Connective tissue was removed from epidermis by means of 0.1% collagenase or 2% sodium iodide in the preparation of cleared unfixed whole mounts, as described by Hambrick and Blank (JID 23: 437, 1954) Providing comprehensive visualization of the epidermal pattern such preparations demo strated the pilosebaceous apparatus as a whole and confirmed the existence of the epidermal eccrine sweat duct unit. The McManus-positive cuticle of the sweat duct could be traced as a continuous lining of both the straight dermal and the coiled epidermal parts of the duct up to the level of the keratinized portion.

Dermis.—The dermis is the layer of fibrous and elastic tissue which underlies the epidermis. Its thickness, ranging from 0.3 to 3 3 mm., is least on the eyelids and prepuce and greatest on the soles, palms and back. The superficial, papillary portion supports the epidermal basal layer and is intimately attached to it. The line of attachment, or basal membrane is of disputed structure but probably is fibrillar (Szodoray ADS 23 920 1931) Nutrient exchange occurs through the medium of tissue juices, for the epidermis is avascular The basal epidermal cells rest on the dermis, and the conjunction consists of many short pedicles or rootlets which interlace with the felt of reticulum and fine collagenous fibers of the papillary layer

The papillary layer of the dermis consists of finely felted collagenous bundles forming rounded projections upon which the epidermis rests. Within these connective tissue projections, numbering perhaps 100 to each square millimeter of surface (Sappey Traité d Anatomie Descriptiv Paris 1877) are capillary loops, nerve fibers and special nerve endings, as well as a lacy net work of fine elastic tissue fibers.

The deep portion of the dermis, the reticular part, consists of dense interlacing bundles of white fibrous tissue and merges beneath with the subcutaneous tissue. Slender branching strands of yellow elastic tissue are threaded through it, surrounding sebaceous and coil glands, hair follicles and blood vessels. Larger fibers of elastic tissue are in the deeper part of the dermis, and small fibers form a fine network close beneath the epidermis, but the reticular fibers of the dermo-epidermal junction are demonstrably distinct from elastic tissue according to Dick (JAnat 81 201 1947)

Collagen fibers apparently take form in an extracellular medium under the influence of factors elaborated by the fibroblasts (Day JPathBact 43 49 1936) Vascular endothelium may also have an active part in the production of argyrophilic connective tissue substance Chronic lymphatic obstruction may lead to massive fibrosis. Electron microscopy of collagen fibers

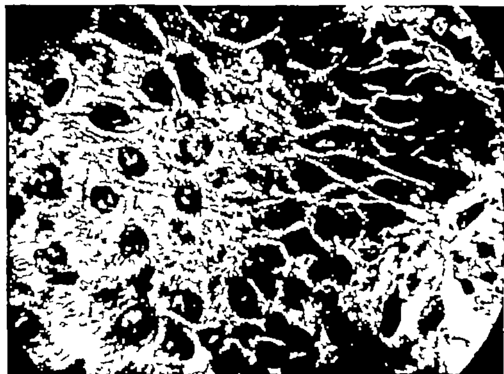


Fig 5.—Epithelial bridges of stratum germinativum, the basal layer of the epidermis lying to the right. (Dr H. Pinkus.)



Fig. 6—Connective tissues of normal dermis collagenous bundles, fibrous tissue cells and small vessels. (Dr H Pinkus.)
Fig 7—Arteriol nerve and venule in deep part of normal dermis. (Dr H. Pinkus.)

shows axial repeating periods of from 500 to 800 A.U., while fibril width ranges from 700 to 1400 A.U (Gross and Schmitt JExpM 88 555 1948) See Randall, edit. (Nature and Structure of Collagen, Academic Press, 1953)

Elastic tissue in branching strands surrounds the bundles of fibrous and muscle tissue glands, follicles and vessels. Lynch (ADS 22 67, 1934) observed their genesis as early as the third fetal month. Their function in hold



Fig. 1.—Skin from chest, showing lanugo hair; elastic tissue is stained black. (Dr H. Pinkus.)



Fig. 2.—Elastic tissue of the papillary portion of the dermis. (Dr H. Pinkus.)

ing the skin together is attested by their absence in epidermolysis bullosa, a disorder in which the epidermis is easily separated from the dermis presumably because of the lack of elastic tissue (Engman and Mook JCutD 24 55 1906) Elastic fibers begin as tiny fibrils which mature in morphology and tinctorial reaction slowly functional demands playing an important role in their development even in embryologic sequences, according to Hass (APath 27 334 583 1939)

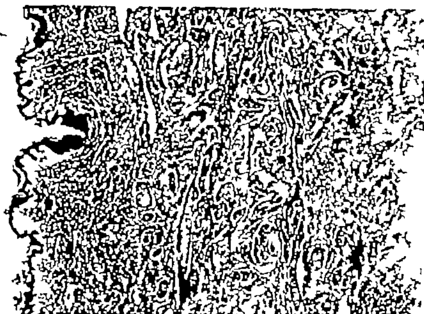


Fig 16.—Skin from the areola of the nipple, showing smooth muscle tissue in the dermis (Dr H. Pinkus.)

Pigment.—The brown hue of the skin is due to an amorphous substance melanin. It is the melanin of the epidermis not that more deeply located, which gives the skin its color (Gates and Zimmermann JID 21 339 1953) Melanin is present as intracytoplasmic granules in the basal cells of the epidermis and in argyrophile dendritic cells capable of ameboid movement. These dendritic cells melanocytes, occur in the epidermis and also in the dermis. Some of them do not contain melanin but contain precursor oxydase granules *that react on treatment with dopa, dihydroxyphenylalanine* changing it to melanin (Bloch AfDuS 124 129 1918) Melanin is a chromoprotein, iron free probably a metabolite of pyrocatechol Pigment production is increased by many forms of irritation and inflammation the increment being conspicuous in persons capable of generous formation of pigment especially in Negroes. Some kinds of inflammation result in depigmentation. Pigment granules are carried to the epidermis, and they may also be carried from it (Becker ADS 16 259 1927, Clin 3 886 1944)

The recommended terminology of pigment cells (Fitzpatrick and Lerner Sci 117 640 1953) is as follows melanocyte means the mature melanin forming cell melanoblast signifies the immature melanin forming cell macrophage or melanophage applies to a *cell containing phagocytized* melanin and melanophore is the contractile cell.

Melanoblasts probably originate from the neural crest of the embryo and wander outward to permanent locations (Becker: Clin 3 886 1944) The neural crest separates from the dorsal pole of the medullary tube and is the matrix of the spinal ganglia, the autonomic nervous system and the chromaffin tissue as well as the melanoblasts. These first appear in the fetal Negro skin in the third month (Zimmermann and Cornbleet: JIn D 11 383 1948) From the first they do not resemble ordinary epithelial cells, and transition between these two cell types have not been observed.

Dendritic melanoblasts progressively pervade the epidermis via the intercellular spaces. In the fifth month numerous secondary processes arise from the main dendrites,

and these progressively surround the epidermal cells, which are dopa negative but receive melanin secondarily by transfer from the dendritic processes of the melanoblasts, which become carriers of melanin during the fifth fetal month.

Melanocytes form a syncytial network, according to Findlay (BJD 65: 437, 1953) in substantiation of the findings of Munch (ZtschrAugenheil 1..: 525 1904). Their cytoplasm contains numerous fibrils lying in the long axis of the cell and in a zigzag or spiral pattern across it. Fine granules of melanin are arranged in an intimate relation with the fibril pattern. Spectrophotometric studies indicate that the color depends on an optical combination of melanin with collagen, the blue color of the iris being attributed to reflection of blue and absorption of violet by collagen, combined with absorption by melanin of much of the light on the red side of blue.



Fig. 11.—Melanin pigment in basal cells of Negro epidermis. (Dr. H. Pinkus.)

M la ocytes are seen in routine sections of normal adult skin usually in the form of clear cells loc ted in the basal layer, where they exhibit smaller darker nuclei and paler cytoplasm than epidermal cells. The afibrillar and shrunken cytoplasm may result in an appearance as of a hole between the palisaded basal cells of the epidermis. Clear cells may be sparse or n merous thei number being not related to the degree of pigme tation. Their long, branching dendrites extend fa in the intercellular spaces while the small body of the melanoblast remains wedged in or just below the basal layer.

Solar pigmentation seems to be related to oxidation (Miescher and Minder: Strahlenthe 66 6, 1939). Tyrosinase in human skin possesses a role in the formation of melanin (Fitzpatrick et al.: Sc 112: 223, 1950). When small areas of black and white skin in guinea pigs were interchanged by full-thickness grafting there occurred depigmentation of previously pigmented skin, while pigment appeared in the host skin at the edge of a pigmented graft (Lewis a d Pecks JInvD 4: 483, 1941).

Inheritance of skin color in human beings apparently takes place by blending (QMN: J 119 1235 1942).

Carotenoid substances give rise to the yellowish hue (Edwards and Duntley AmJAnat 65 1 1939). Blood in the superficial capillaries is the source of the reddish color. Dilation of capillaries increases intensity of redness. Compression, constriction, collapse, and atrophic diminution in the number of capillaries, and anemia result in pallor.

Lymph Vessels form a superficial plexus in the papillary part of the dermis, and in the subdermal layer a deep plexus communicates with the trunks which follow the subcutaneous blood vessels. The superficial plexus is so abundant that injections in the lymphatics are absorbed almost immediately. While particulate matter is not perfused through the walls, slight trauma causes great increase in permeability as do heat, light and chemicals also (Hudack and McMaster JExpM 57 751 1933).

Blood Vessels.—A rich supply of blood is maintained by two parallel horizontal systems of vessels, the subpapillary and subcutaneous plexuses.



Fig. 11.—Vermilion border of the lip blood vessels injected. (Dr H. Pinkus.)

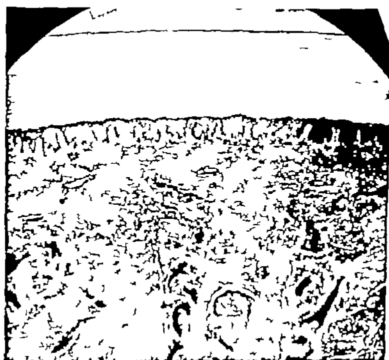


Fig 12.—Transverse section of nail and nail bed, blood vessels injected (Dr F O Harris.)

From the superficial plexus, capillary loops extend into the tips of the papillae Numerous branches of the deep plexus supply the hair follicles sebaceous glands and coil glands. (Clark and Clark Am J Anat 64 [illegible]1 1939)

Myoarterial Glomus.— In the pulp of the fingers and toes, the palms and soles, and elsewhere in the body there are special organs which function as arteriovenous anastomoses. In a glomus the afferent arteriole divides as it approaches the surface part going to the skin and part by way of a thick

walled neuromuscular glomus to a venule. These Suequet Hoyer canals are normal and functional parts of the vascular system serving to control the acral circulation

Nerves of the skin follow in general the course of the blood vessels. There are medullated and nonmedullated fibers. The main trunks run horizontally in the subcutaneous tissues and give off branches which divide and pass into the dermis with the arteries from the subcutaneous plexus. Slender branches pass into the papillary bodies, and some terminate there in special end organs. Nonmedullated fibrils are distributed to the endothelium of the capillaries and also pass through the papillae lose their sheaths, and terminate on the cells of the epidermis. Skin innervation is beautifully illustrated in the article of Weddell (BMBull 3 733 1945) Free sensory endings are often ball or knob-shaped. *Merkel has described tactile cells which are found in the deeper* layers of the epidermis, especially numerous in the epithelium of hair follicles. Nevi seem to be collections of anomalous cells of this type (Ebert ADS 37 1 1938)

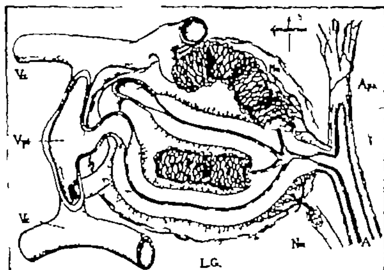


Fig. 14.—Glomus: neuromyoarteriovenous anastomotic organ, schematic. *A*, superficial preterminal artery. *Apa*, terminal branch entering capillaries. Side branch is afferent artery entering the glomus dividing into 4 neuromuscular arterioles. Elastica of afferent arteriole disappears as arteriole enters glomus. Wall of vessel becomes thick due to increase in smooth muscle fibers, which terminate abruptly at beginning of venous segment. Efferent glomic vein leads into a collecting vein (*V. pc.*) which is dilated and thickened at the junction; and it leads into superficial vein, *V.s.* *Nm* is rich perivascular network of nerves, connected with periarterial sympathetic nerves as well as myelinated sensory nerves (*Nm*) to the skin. *L.G.*, connective tissue capsule. (After Masson, Ourbitson and Tennant: Surg. 5 84, 1939.)

Hair follicles receive nerve supply in a manner similar to that of the epidermis the fibers passing into the prickle-cell layer of the follicle.

Several types of encapsulated nerve endings occur the tactile corpuscles, or corpuscles of Meissner the end bulbs of Krause and of Pacini, the genital corpuscles, and the terminal cylinders. The corpuscles of Meissner are small, oval structures from 80 to 150 microns long and about one-half as broad. They are found in sensitive regions the palms, soles, lips nipples penis, and clitoris, and dorsums of the hands and feet They generally occupy the tips of the papillae their long axes perpendicular to the surface. Pacinian corpuscles are not confined to the connective tissue of the skin but are also found in many other parts of the body These bodies are large oval, onionlike structures, which range from 0.5 to 2.0 mm in length They possess a thick capsule composed of from one to three dozen concentric layers of fibrous tissue and a core of granular semisolid material in which the naked axis cylinder is embedded.

Evidence indicates that the end organs of Krause are cold receptors, those of Ruffini are warmth receptors, and those in hair follicles are touch receptors, while free endings mediate painful stimuli. Tactile fibers are myelinated, pain *and thermal fibers nonmyelinated. One nerve fiber carries* only one kind of endings (Woollard JAnat 71 54 1936 Zotterman JPhys 95 1, 1939 Kuntz and Hamilton AnatRec 71 387 1938) The doctrine of specificity of

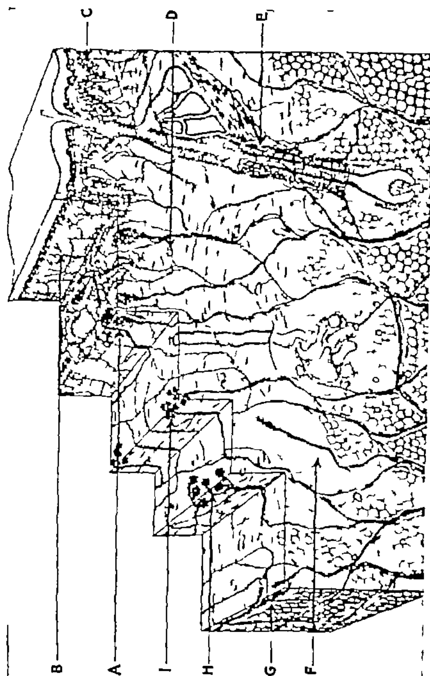


FIG. 16—Cutaneous innervation, schematic. *A* groups of Meissner corpuscles subserving the sensation of touch *B* beaded nerve nets subserving pain (probably fast pain) *C*, Merkel discs subserving touch; *D* beaded nerve fibers derived from nerve nets subserving pain and associated with blood vessels (probably slow pain) *E* nerve terminals around the sheath of a hair subserving touch *F*, a pacinian corpuscle subserving pressure *G* a group of Ruffini endings subserving warmth H and I, groups of Krause's end bulbs subserving cold (these lie at somewhat variable depths beneath the skin surface) *Note*—The organized endings are accompanied in every instance by fine-beaded nerve fibers subserving pain. (Weddell HMBull 3 187 1945)

nerve function is supported clinically physiologically and anatomically (Walshe Brain 65 48 1942) of the 4 primary modes of sensation touch pain, cold and warmth each is a sensory unit with end organs disposed in the skin in area and in depth such that activation of a spot influences the whole unit Pain is the *sense mediated by all on extreme excitation. The anatomy* of cutaneous sensibility was well set forth in Edit. (BMJ 2 342, 1942)

Nocifensor System.—The existence in the skin of an intrinsic neural system, a posterior root system the axones of which arborize freely in the skin, has been postulated. Vascular flares at the sites of injury apparently are due to the vasodilating influence of these nerves, for the flare reflex, normally provoked by pricking the skin through a droplet of histamine solution persists only 5 to 7 days after a cutaneous nerve is cut. The histamine test is useful to test the integrity of cutaneous nerves, as in leprosy Histamine



Fig. 16.—Meissner' corpuscles in dermal papillae of finger (Dr H. Pinkus.)

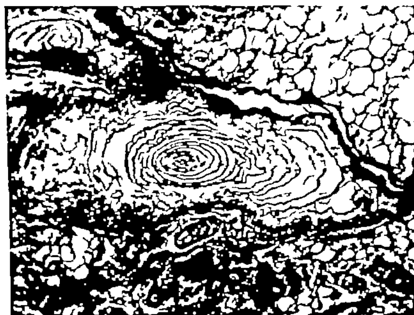


Fig. 17—Vater Pacini corpuscle of finger tip. (Dr H. Pinkus.)

provokes whealing, but not erythema, after degeneration of the nerve (Lewis BMJ 1 431 491 1937; Castello and Tianti ADS 47: 826 1943) No direct evidence of the existence of an independent system of branching axones of posterior nerve root origin could be found by Kuntz and Hamilton (AnatRec 71: 382, 1938)

Muscles of the Skin.—The striated are limited to the superficial voluntary muscles of the face and neck. The nonstriated are abundant, particularly

in the scrotal and perineal regions about the nipples, and in the scalp Ar rector muscles of the hair follicles are bundles of smooth muscle fibers, the contraction of which gives rise to goose flesh

Glands of the Skin.—The glands of the skin are of two types the merocrine and the holocrine In the merocrine glands, eccrine and apocrine secretion takes place without the destruction of cells. Eccrine glands secrete clear fluid and apocrine glands secrete an emulsified milky fluid from the tips of the secretory cells. The secretion from the holocrine glands is the actual dis integration product of the cells themselves. Sweat glands are eccrine or apocrine Fat glands are holocrine

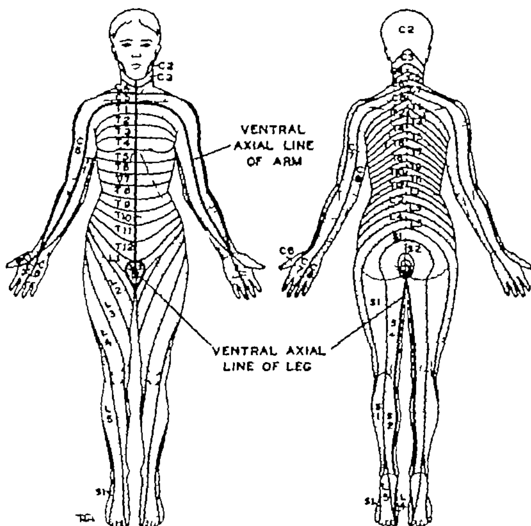


Fig. 18.—Dermatome chart f localization of nerv root lesions (Dr J J Keegan, U i ersity of N braska College of Medicine Anat Rec 102 409, 1948)

Eccrine Sweat Glands, or coil glands, are modified tubular glands which occur on all parts of the body except the margins of the lips the glans, and the inner surface of the prepuce They are most numerous on the palms and soles. Anatomically there are two parts, a body and an excretory duct. The body is globular and consists of windings of an epithelial tube of fairly uni form caliber The secreting or glandular portion of the tubule is composed of a single row of low columnar cells. Their bases rest on a thin layer of myo-epithelial cells the spindle-shaped elements of which are arranged longi

tudinally Surrounding this layer is an external sheath of fibrous and elastic tissue The glandular portion of the sweat coil is supplied with blood from a network which surrounds it

The epidermal sweat duct unit designates a morphologic and biologic entity which includes the intraepidermal portion of the sweat duct a single



Fig 19—Axillary skin and apocrine glands. (Dr H. Pinkus)



Fig 20—Apocrine gland from axilla, and myoepithelial cells. (Dr H. Pinkus)



Fig. 21—Eccrine glands, from forearm. (Dr H. Pinkus)

layer of lining cells the periductal sheath of epidermal cells concentrically arranged about the cells lining the duct and the eccrine sweat pore (Lobitz et al JID 22 157 23 329 1954) See Epidermis, separation of p 5

Two moderately distinct types of cells line the secretory tubules, designated, on the basis of their affinity for basic dyes, as dark ' and ' clear cells by Montagna et al. (JID 20 415 1953) The smaller dark cells contain numerous granules composed chiefly of ribonucleic acid while the clear cells contain only sparse fine granules. Vacuoles and canaliculi, both inter and intracellular are conspicuous only in the clear cells. Both types of cells contain abundant glycogen and numerous mitochondria. The secretory cells have in their cytoplasm lipid granules, mostly pigmented reactive to Baker s test for phospholipid The lipid and the pigment remain sudanophilic even after embedding in paraffin. The cells of the lower portion of the excretory duct abound in ribonucleic acid, glycogen and mitochondria suggesting that the duct itself may have an active secretory or resorptive function.

Histologic variations in normal sweat glands were depicted by Holyoke and Lobitz (JID 18 147 1952)

The nerves consist of nonmedullated sympathetic fibers, which form a close plexus on the outer surface and give off fibrils to the glandular and muscular cells. The duct is a tubule lined with two layers of pavement epithelium It passes through the dermis in a spiral until it reaches the epidermis, where it loses its connective tissue sheath In the stratum granulosum it assumes a corkscrewlike course and opens on the surface. Sweat duct epithelium is distinct from the epidermis, although encased in it (Pinkus JInvD 2 175 1939 AexperZellforsch 22 47 1938 tissue culture)

Apocrine Sweat Glands—Certain large glands, especially of the pubic circumanal, abdominal mammary and axillary regions, secrete fatty and odorous substances as well as sweat They are twice as numerous in the female as in the male They are more numerous in the Negro than in the Caucasian They atrophy with advance of age more than ordinary sweat glands. The distal portion of the secretory cell is discharged with secretion whereas in sebaceous glands the whole cell disintegrates to form the secretory product and in eccrine glands the secretory cell remains intact (Way and Memmesheimer ADS 34 797 1936 38 373 1938)

Investigations of the myoepithelium of apocrine glands confirmed the contractility previously observed reported Hurley and Shelley (JID 22 143 1954) Myoepithelium exists as a sheath of smooth muscle fibers supplied by adrenergic autonomic nerves, with the function of delivering preformed apocrine sweat to the surface of the skin. The gland is in effect a reservoir of sweat which when once emptied, requires several hours before further sweating can be induced by the mechanical thermal electrical or pharmacologic stimuli which ordinarily initiate contraction of smooth muscle tissue Apocrine tubules in vivo manifest peristaltic waves when stimulated. Apocrine gland function may be divided into 2 phases (1) secretion, a continuous activity under hormonal control and susceptible to the effect of intraluminal pressure and (2) sweating a delivery of preformed sweat to the skin surface as a result of peristaltic waves of myoepithelial contraction in response to stimulation which may be mechanical, adrenergic by way of the innervation or humoral by way of circulating epinephrine

Sebaceous Glands secrete oil These are usually but not necessarily, associated with hair follicles. The Meibomian glands in the eyelids are modified glands of this type as are also the smegma glands of the penis. Sebaceous glands occur on all parts of the body except the palms soles, and terminal phalanges A sebaceous gland consists of a fibrous capsule a membrana propria and a collection of epithelial elements. The capsule and lining membrane are continuous with the corresponding layers of the hair follicle and the epithelium is a direct prolongation from either the outer root sheath of



Fig. 22.—Vulvar sweat glands. (Dr H Pinkus.)





Fig 23.—Apocrine gland during secretion. (Dr Stuart Way)
Fig. 24.—Sebaceous gland from nose, not associated with a hair





Fig. 25.—Sebaceous gland (Dr H. Pinkus.)
Fig. 26.—Eccrine gland, elastic tissue stain (Dr H. Pinkus.)

a follicle or the prickle-cell layer of the epidermis. These organs range from small, simple pouchlike alveoli to large lobular racemose structures. The center of the alveolus is filled with larger cuboidal or polyhedral cells which undergo fatty degeneration. The epithelial débris escapes into the hair follicle *or directly upon the surface of the skin and comprises sebum* Sebaceous glands are responsive to endocrine influence and become larger and more active in response to androgen (Rony and Zakon ADS 48 601 1943) See Seborrhea also histochemical studies of Bunting et al (AnatRec 100 61 1948)



Fig 17 —The scalp, X20. (Dr H. Pinkus.)

Unicellular sebaceous glands have been described by Wolff (BMJ 1 588 1951) who observed large clear cells in the basal epidermal layer with contents that are birefringent in polarized light as in ordinary sebaceous glands. They take the fat stains, and their presence accounts for the oily shine on palms and soles from which ordinary sebaceous glands are absent

Hairs are cylindric horny structures derived from the epidermis, implanted in pouchlike depressions in the dermis. They occur on all parts of the body except *the palms and soles, penis and terminal phalanges. There* are 3 classes of hairs (1) vellus or fine soft hairs (2) long hairs as those on the scalp pubes, bearded region, and axillae and (3) short, stiff hairs, such

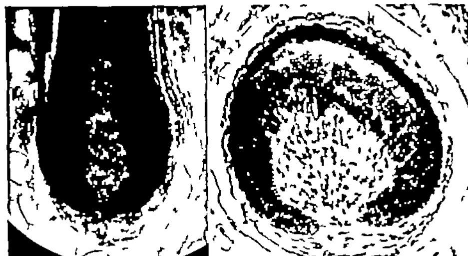


Fig. 28.—The hair papilla.
Fig. 29.—Papilla of a growing hair of the scalp. (Dr H. Pinkus.)



Fig 30.—Scalp hair cross section at deep level. (Dr H. Pinkus.)
Fig. 31.—Scalp hair cross section at superficial level. (Dr H. Pinkus.)



Fig 32.—Arrector pili muscle the epidermis lies to the right.

as are found on the eyebrows and eyelids. A hair consists of a shaft and a root, which is embedded in the skin. The cortical substance of the shaft is composed of flat, nucleated, epithelial cells. The medulla of the shaft is filled with cells which contain more or less pigment. Air spaces are present in both cortical substance and medulla. Externally the shaft is covered with a thin, semitransparent, shiny cuticle composed of flat imbricated cells. On transverse section straight hairs are circular and curly and kinky hairs are elliptical.

As the hair grows outward from its papilla the epidermis of the inner root sheath grows outward with it at the same rate (an "effluvial current" of epidermal growth Wilson called it) and the internal root sheath desquamates at the level of the sebaceous gland above which keratinization is like that of the epidermis (Kligman AD 71 313 1955)

SHEDDING OF HAIRS is normal and continues throughout life. Each hair is exchanged at intervals of several months. When a hair is about to be shed, cornification of the root extends down almost to the papilla, the bulb splits into fibrils, the hair separates at the papilla, and the follicle becomes constricted at this point. As the exfoliating hair pushes outward and falls away a new matrix develops by outbudding from the side of the old follicle. See Chase (PhysiolRev 34 113 1954) Montagna and Chase (AnatRec 118: 330 1954)

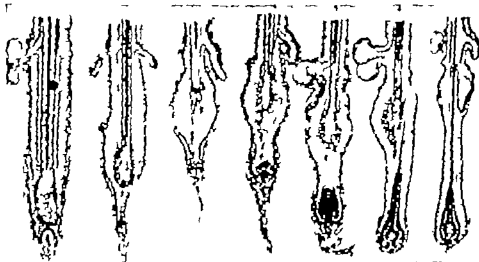


Fig 13.—Regeneration of hair (after Unna) (Pusey Principles and Practice of Dermatology ed 4 D Appleton-Century Company)

GROWTH AND DISTRIBUTION OF HAIR are little understood. Hypertrichosis is found in hypopinealism, hyperpituitarism, hypergenitalism and hyperfunction of the cortex of the suprarenal gland. With endocrine disturbances, there are striking differences between men and women in the growth and distribution of the hair. Hypopituitarism causes the male to assume the female type of distribution of hair but it does not cause the female to assume the male type of distribution. Hyperpituitarism, on the other hand, causes the male to become more masculine in type and the female to become masculine in type. Hyperplasia or tumor of the cortex of the suprarenal gland also causes the male to become more masculine in type of distribution of hair and the female to assume the masculine type of distribution of hair. Vitamin A, thyroid, estrogen and iron metabolism are much concerned with hair texture and its degree of oiliness or fragility.

See Copley (Sci 105 340 1947) physical properties of hair; Marchionini and Dracsche (DWchn 107 91 1938) changes in tensile strength and elasticity in metabolic diseases; Dieke (Endocrinol 40 123, 1947) rhythmic alterations of growth of individual follicles in animals, and investigation of effects of altering adrenal and pituitary glandular balance; Beek (Dermatologica 101 317 1950) distribution of hair in human beings; Odland (JID 21 305, 1953), histochemical studies of keratinization, showing distribution of thiol and disulfid groups and of ribonucleic acid

Nails are flat horny plates which overlie the ends of the dorsal surfaces of the fingers and toes. They are composed of modified epithelial tissue. The nail root is firmly embedded in the nail groove, a pocketlike recess of the dorsal digital skin. The nail plate is composed of flattened corneous cells and together with its underlying epithelium is supported by the dermal nail bed.

The proximal root is largely the productive portion of the appendage and is the zone of distad growth (see Nail growth and manifestations of abnormality) The root from which the nail grows is concave proximally As nail plate grows distad it matures in keratinization only after it has pushed distally several millimeters. The immature nail substance slightly milky shows as the lunula just distal to the proximal nail fold and is concave proximally paralleling the root from which it grew The lunula may be abbreviated, and it may lie entirely beneath the nail fold although this is not common The lunula is more often absent in the Negro than in white persons (Harris ADS 61 115 1950)

The nail bed and plate grow forward together as evidenced by the fact that a subungual clot grows out with the nail, so that the outgrowth cannot be interpreted as a mere gliding of the plate over the bed (Silver and Chicgo JInvD 3 133 1940) Connective tissue fibers in the subungual region are arranged both vertically and horizontally Vertical fibers extend from the periosteum to the undersurface of the nail bed and bind the nail firmly in place.

The rate of nail growth varies. It is said to be most rapid in the young and during the summer months, amounting to about 1 0 mm. per week (Clark and Buxton BJD 50 221 1938) The rate of growth of the thumbnail ranged from 0 112 to 0 172 mm per day without seasonal variation but with gradual slowing over a ten-year period, noted Bean (JID 20 27 1953) regarding his own nail In right handed individuals the rate of nail growth is somewhat faster on the right hand than on the left, according to Wigand (abs ADS 38 961 1938)

The structure and development of the fetal and adult nail were described by Lewis (ADS 70 732, 1954) see Nails, growth and abnormalities of (p 1349)

Epidermis is from an early age an ectodermal vestment of two layers. The epitrichium, a surface layer of flattened horny cells, corresponds to the corneum of the adult even in chemical reactions (Unna). From a single layer of stratum germinativum which rests upon the mesoderm destined to become dermis is derived by mitotic proliferation the multilayered epidermis. During the third month parallel ridges arise from the lower surface of the epidermis first upon the fingers, palms and soles and sweat glands later grow by downward budding from these into the dermis. On parts to be covered by hair comparable ridges develop in a network of star like pattern, and the primordia of the hairs arise in them.

Dermis and Hypodermis during the first six weeks consist of ordinary mesenchyme. In the second month fibrillar interstitial substance begins to be produced elastic fibers appearing later. The mesenchyme becomes apportioned into a superficial compact layer and a deeper loose one which is to be the subcutaneous tissue. The dermis further differentiates into a peripheral papillary layer and a deeper reticular layer in which the collagenous bundles become thick, interlaced and disposed in a direction predominantly parallel to the skin surface.

Hairs are first manifest in the eyebrow chin, and upper lip regions at the end of the second month. Proliferating cells appear in groups in the stratum germinativum. The growth of such a hair germ into the dermis produces a gradually elongating compact epithelial cylinder. Under it the connective tissue is condensed and the hair papilla so formed protrudes from below into the epithelial cylinder. The direction of the latter is not perpendicular to the skin surface. On that side of the cylinder where the angle is obtuse there develop two rounded projections. In the upper of these the central cells undergo fatty transformation and their further development produces the lobed outpouching from the hair follicles which is the sebaceous gland. The lower projection from the cylinder is the place of attachment of the arrector muscle which differentiates in the adjacent mesoderm. Within the bulb of the cylinder which caps the hair papilla a central cone of cornifying cells differentiates. These push upward by the multiplication of the cells on the summit of the papilla and so form the hair shaft.

Nails are earliest evidenced as flat areas on the backs of the terminal phalanges during the third month. These primary nail fields are surrounded by a fold, deeper grooved on the proximal side. Not until the fifth month is the true nail substance produced in the proximal nail groove the deep epidermis being transformed into nail matrix. Its cells become penetrated by fibrils of onychogenic substance and are flat and closely adjoined. As the thin nail plate moves distally within the epidermis, the overlying layers are desquamated until the plate is fully exposed being covered later only by the proximal fold. See Anatomy nails

Sweat Glands are seen earliest on the palms and soles in the fifth month. In their downgrowth the shaft is elongated and the lower portion curls in the form of a ball. A lumen forms in this secretory part in the seventh month and another lumen develops in the excretory portion of the duct to unite with it. The epithelium around the lumen forms two layers which differentiate in the secretory portion into an external layer of flat myoepithelial cells and an internal layer of cuboid glandular cells.

See Pinkus (in Keibel and Mall Manual of Human Embryology Lippincott, 1910 vol 1, p. 243) development of the integument (ADH 21 331 1911) sebaceous gland Kuettner and Wiser (ADH 26 331 1932) hair Narhol ... Kus ... (Proc N Academy ... 1936) rat embryo tissue culture Huxley and DeBeer (Elements of Experimental Embryology Cambridge Univ Press, 1934) W y and Mennmeshimer (ADH 34 787 1936) sweat glands, Spemann (Silliman Lectures Springer Berlin, 1936) the organizer Leslie-Roberts (JUD 31 405, 431, 1949) growth of epithelium Hamburger (Manual of Experimental Embryology Chicago Univ Press, 1942) Maximow and Bloom (Textbook of Histology Saunders, 1942)



Fig. 14.—Skin of 3-month human embryo. (Dr H. Pinkus.)

Fig 15.—Skin of premature from toe, showing regular pattern of cristae cutis and sweat ducts. (Dr H. Pinkus.)

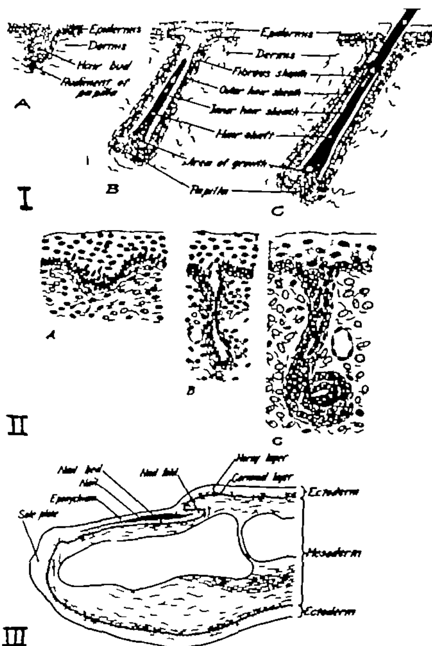


Fig. 34.—*I* Development of hair (*A*) early stage of bud, (*B*) hair has differentiated within axis of bud and is growing toward surface (*C*) hair fully developed. *II* Stages of development of sweat gland *III* Longitudinal section of nail of fifth-month fetus, diagrammatic. (Dodds, G. S. Essentials of Human Embryology John Wiley & Sons, Inc.)



Fig. 37.—Hair germ of 14-day rat fetus. (Dr Margaret Murray.)
Fig. 38.—Hair germ of 16-day rat fetus. (Dr Margaret Murray.)



Fig. 39.—Sensory hairs from face of 16-day rat fetus, having grown 4 days in vitro. Follicles have developed in the explanted skin, showing normal topography in vitro, mechanical obstruction having been avoided. The hair organ is formed by growth and differentiation of groups of cells already determined as to morphologic and dynamic potencies. Pigment makes its first appearance in the epidermis of the hair bulb, just above the dermal papilla. (Dr Margaret Murray.)

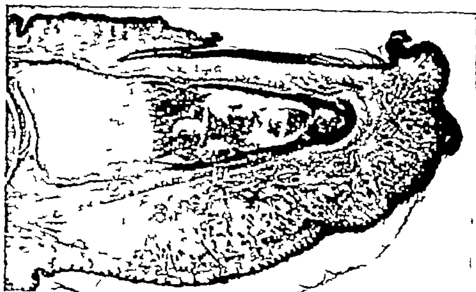


Fig. 40.—Longitudinal section of digit of premature. (Dr H. Pinkus.)

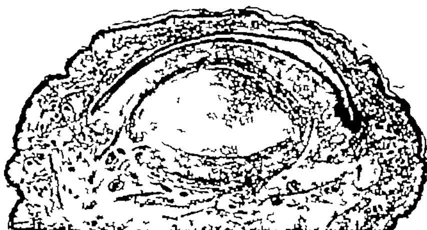


Fig. 41.—Transverse section of digit of premature, cutting nail proximal to proximal nail fold. (Dr H. Pinkus.)



Fig. 42.—Nail of premature. (Dr H. Pinkus.)

The skin is the dividing line between the individual and his environment It is primarily a barrier It serves in protection sensation heat regulation and chemical exchange with the exterior As an organ of three times the weight of the liver its functions concerned with water nitrogen glycogen and vitamin metabolism and with inflammatory and immunologic activities are significant. See Rothman (Physiology and Biochemistry of the Skin, U of Chicago Press, 1954)

Protection.—The insensitive insoluble fat-covered and relatively inert horny layer with its underlying regenerative epithelium resists abrasion, light, heat and living organisms and the tough resistant dermis on its springy elastic base of fibrous and adipose tissue admirably absorbs extrinsic forces and displacements. Light is reflected or absorbed by pigment Heat is radiated by increased blood flow On a dry healthy skin the number of bacteria and yeasts is reduced by 75% in 10 minutes and 95% in 30 minutes (Cornbleet and Montgomery ADS 23 908 1931)

The pH of the skin surface of children averaged near 4 0 for all age groups on the scalp chest and extensor aspects of the forearms but was higher in the axillae and between the toes (Herrmann et al JID 7 215 1946) The normal range of pH in adults was from 4 0 to 7 0 (Blank JID 2 67 75 231 235 1939) the extensor surfaces of the arms being more alkaline than the flexural, and the antecubital the most acidic region There was more variation between individuals than between males and females. The pH diminishes on hot days and increases following the use of soap (Bernstein and Herrmann: NYSJM 42 436 1942) The pH is relatively alkalinized by bathing but returns to normal after a few hours (Arbenz Dermatologica 105 33 1952)

Alkali neutralization and alkali resistance of the skin may be tested. Wacek (Dermatologica 107: 369 1953) studying these aspects of the cutaneous protective mechanisms in normal and eczematous subjects, used a modification of Burckhardt's method: he placed a drop of fresh N/[illegible] NaOH onto 3 areas of the forearm or arm, and after 10 minutes cleansed the skin and examined it. If no reaction had occurred, he repeated the procedure on 2 of the 3 same areas. Finally he reapplied NaOH on 1 of these 2 areas so that he might compare reactions on areas tested with exposures of 10 20 and 30 minutes respectively Alkali resistance was found decreased in cases of cement dermatitis, housewives eczema, and ichthyosis. Alkali and acid neutralizing powers were found to be parallel. Barriers included sebum, sweat corneum, perhaps the bicarbonate buffer and finally tissue fluid if the epidermis were broken.

Skin Flora.—Microorganisms of many kinds are found on the skin but those which constitute the skin flora have little invasive power Some of them may be able to attack only when mechanical or chemical injury or altered physiologic integrity renders the skin more vulnerable When a pathogen is present, however as in furunculosis or infectious eczematoid dermatitis virulent organisms are available over the whole surface so that a minor abrasion promptly becomes infected. Pathogens may be present transiently the streptococcus being it is thought, always either a pathogen or a transient. The dermatophytes are capable of utilizing keratin, despite the fact that it is chemically inactive this advantage over other fungi forms the basis of their pathogenicity (Benham and Hopkins ADS 28 532, 1933) Hydration or alkalinization increases the flora while dehydration or acidification diminishes it (Arnold JID 5 207 1942) In the presence of pyogenic dermatitis, pathogens may be found widespread on noninvolved skin (Martin BMJ 2 245 1942) See also Pillsbury et al (ADS 45 61 1942) Pillsbury and Nichols (JID 7 365 1946) Rebell (JID 8 13 1947)

There are a few types of bacteria that seem to multiply freely on the skin and particularly in the sebaceous glands these can generally be culti

vated without difficulty The most important of these are the gram positive cocci. Of the numerous types that have been described, much the commonest is the white pigmented variety *Staphylococcus epidermidis albus* Another variety is found very frequently in scurf, and is known as Gordon s scurf staphylococcus. Occasionally yellow pigmented staphylococci are found, and sometimes sarcinae The great majority of cocci found on the skin are com paratively nonpathogenic both to human beings and to rabbits but a few consist of the pathogenic golden variety This variety constitutes 3 to 5% of the total colonies developing on blood agar plates which have been pressed against the normal skin whereas the white staphylococci constitute 90% Amongst the other organisms met with are occasional coliform and Proteus bacilli and diphtheroids. The healthy skin appears to have some natural self-disinfecting mechanism In the skin lining the external auditory meatus, as well as the usual staphylococci diphtheroid bacilli are not uncom mon and sometimes saprophytic acid fast bacilli, derived from the cerumen, are met with This quotation is from Topley and Wilson (Principles of Bacteriology and Immunity Wood 1937 see pp 801 1550)

Cultural studies of normal skins by Evans et al (JID 15 305 1950) revealed anaerobic bacteria outnumbering aerobic by from 10 1 to 100 1 *Micrococcus epidermidis* *Staph albus* and *M candidus* were regularly present while orange strains of *Staph aureus* were rare. *M flavus* was infrequent and *M citreus* was never found. *M saccharolyticus* was present in large numbers and was the predominating organism in some individuals. The sebaceous glands appeared to be the major site of bacterial luxuriation. No bathing for a week did not significantly increase the bacterial population.

DISINFECTION can be accomplished effectively by scrubbing which reduces the flora by 50% each 6 minutes, according to Price (JInfectD 63 301 1938) Hands and arms thoroughly degermed may require a week for com plete re-establishment of the usual flora Beneath rubber gloves the existing flora increases rapidly Drying accounts for much of the mortality of *Str hemolyticus* when it is put onto the skin, and the acidity of the sweat is also important (Burtenshaw JHyg 38 575 1938) Mechanical cleaning defat ting and germicides are all needed for sterilization and Merthiolate is ef fective according to Magath (SCNAm 20 931 1940)

The skin of the newborn sterile at birth is best let alone The baby should be kept away from infection and infection kept away from the baby urged Klein and Aries (IllMJ 77 337 1940)

SELF STERILIZATION of the skin has been studied intensively but is not fully understood Norton and Novy (AmJPH 22 193, 1932) believed that drying is the main factor that accounts for it The acidity of the sweat plays a role and the high concentration of free fatty acids was adjudged significantly related to the germicidal properties of the skin surface by Engman and Kooyman (ADS 29 12 1934) Fungistatic and fungicidal actions of sweat and its chemical fractions were investigated by Peck et al (ADS 39 126 1939) Concentrated sweat they reported fungicidal even if alkaline due to its content of acetic propionic caproic capyrylic lactic and ascorbutic ions Yet Cornbleet and Meyer (NEngJM 230 604 1944) cultivated fungi on sweat and sweat-agar mediums Disinfection can be attributed to at least 5 mech anisms (Burtenshaw BMBull 3 161 1945) drying acidity fatty acids of the sweat light and some other factor which is enhanced by a ketogenic diet According to Ricketts et al. (ClinSci 10 89 1951) drying is the major factor influencing *Ps aeruginosa* and *B coli* unsaturated fatty acids inhibit *Strept pyogenes* and both of these agencies affect *Staph aureus* Drying diminishes resident as well as transient bacteria observed Pillsbury and Rebell (JID 18 17 1952) who found gram negative rods somewhat more resistant than normal skin micrococci to certain fatty acids. Normal skin organisms grow well in the normal pH range of from 5 to 6 excepting the aerobic diphtheroids which do not tolerate much acidity

Sensation.—Sensory end organs are distributed over the skin in a puncti form manner Areas most sensitive to heat and cold are found on the lips, tip of the tongue and eyelids. Pressure points are close to hair follicles and on nonhairy regions probably depend on the tactile or Meissner corpuscles in the papillae They are more numerous and smaller than hot and cold points. Pain sense is disseminated generally and is also punctiform in distribution the free sensory ending is probably its receptive organ Surface pain is ac curately localized Sensory spots on the skin must be distinguished from end organs themselves, for Gilmer and Haythorn (ANeurl 46 621 1942) did not find nerve endings under pressure vibration spots, and Weddell (JAnat 75 346 441 1941) showed that sensory spots overlie more than one ending or group of endings of the same type and that nerve fibers subserving the spot are separate and multiple More than one Krause end bulb may hang on one nerve fiber and a terminal network for pain may spread over a circular area almost 1 cm in diameter

The pricki g pain of momentary stimulation by heat needle prick or pulling of a hair cannot be distingui hed, while burning pain is the identical se sation differing only in its duration, according to Lewis (BMJ 1: 321 1938) Skin pain is only a single quality of sensation with variation in intensity a d duration; it is a sharp pain which quickens reflexes a d, within limits, invigorates The ache-pain of muscle o tendon pain dull reflexes a d sickens. Prick-burn sensation and ache-pain are of completely different qualities of se sory experience Lewis beli ed. No co relation between itching and pain thresholds could be demonstrated by Potel na et al. (JID 1 : 307 1949) They believed that itching and superficial pain must result from different causes nd possess different sensory identities. The adequate stimul for pai is tissue injury (Hardy et al.: Sci 114: 149, 1951; Wertheimer and W rd: Sci 115 499 1953) An algesimeter using f radio stimulation pplied to the ear lobe was so devised by Siker et al. (Sci 1*0: *73, 1954) to give reproducil le results.

Itching and pain are apparently mediated by the same receptors and fibers, argued Rothman (The Nature of Itch ng Williams and Wilkins, 1943) because in pathologic cases of sensory dissociation, the perception of itching disappears and reappears with the per ception of pain. When complete tactile anesthesia is associated with unimpaired pain sense the itching sensitivity is likewise unimpaired. Pain and itching paint has the same density of skin di tribution and they cover each other Tickle becomes itch, and itch becomes burning pain with increase of stimulation. The sensation experienced depends on the frequency of impulses in the slowly cond cting C fibers of Gasser and Erla ger Itching was experimentally produced and studied by Bi hop (JID 11: 143, 1948) It appeared to result from a persistent exitation insufficiently intense to cause pain and too con tinuous to register as prick. It could be induced by the summation of weak electric shocks individually below the prick threshold. Investigating pruritus induced by intra dermal injection of histamine Cormia and Kuyke dall (JID 20: 429 1953) found that the sensation of itch changed to burning and pain if the stimul s was tripled. See Hardy et al. (Pain Sensatio s and Reactions, William and Wilkin 1952) who noted that aspirin in small dosage effectively raises the heat pain threshold.

Nerve impulses induced by discharge of single warm and cold fibers in the tongue of cat and dog were recorded by Zotterman et al. (AnnRevPhysiol 15: 357 1953) See Geldard (The Human Senses, Wiley 1953) containing 3 ch pters on cuta eous sensibilities.

Referred pain from internal disorders is referred to the region of the surface distribution of the same or adjacent somatic neural segments.

Nerve injury which denervates and so diminishes sweating results in in crease of electric resistance of the skin, and the mapping of skin resistance may be used to delineate denervated areas accurately (Richter and Katz J 122 648 1943)

The acetylcholine axone reflex is located in the skin according to Roth man and Coon (JID 3 79 1940) Acetylcholine mediates propagation of impulses across ganglionic synapses in the autonomic nervous system. All preganglionic sympathetic nerve fibers liberate the substance at their end ings. Postganglionic fibers are of two kinds those which liberate acetyl choline and those which liberate sympathin. Cholinergic and adrenergic fibers are not completely parallel in the sympathetic and parasympathetic systems. Cholinergic fibers include (1) all preganglionic fibers of both sympathetic and parasympathetic systems, (2) all postganglionic fibers of the parasympathetic system and (3) postganglionic sympathetics of the eccrine glands. All other sympathetic fibers are adrenergic Epinephrine and

sympathin act on effector cells, whether an organ is denervated or not. Pilomotor fibers are stimulated by sympathin, which can be demonstrated in the circulation after stimulation of the sympathetic chain. Ergotamine blocks the action of sympathin. Atropine inhibits the action of acetylcholine while physostigmine intensifies it. Eccrine sweat secretion is elicited by acetylcholine paralyzed by atropine. An adrenergic component probably exists, capable of being inhibited by ergotamine and other adrenergic blocking agents.

HISTAMINE TEST FOR NERVE FUNCTION.—A simple test for nerve function depends on the kind of reaction which results from the intradermal introduction of 0.01 cc. of 1:1,000 histamine HCl. One punctures the skin at half-inch intervals and applies a drop of the histamine solution. The wheals which result are surrounded by intense flare if the nerves are intact and there is no flare if they have degenerated. The absence of flare in degeneration may precede by several days the electrical reaction of degeneration. A nerve root lesion gives a negative test, a spinal cord lesion gives a positive one. The test is valuable in differentiating hysteria and malingering from neural lesions and in problems of accurate localization.

The flare resulting from intradermal injection of histamine was a good criterion of the integrity of the peripheral sensory axones plus adequate peripheral circulation, Bereston (JID 6 3 1945) concluded in a study correlating skin responses with central nervous system lesions. The pilomotor reaction to intradermal acetylcholine was a criterion of the integrity of the peripheral sympathetic axones. The intensity of reaction was diminished in persons with neurologic defects and this was true of the flare reactions, but not of the papular reactions to tuberculin and trichophytin in these persons. The reaction to ultraviolet light, however, was greater in defective skin, while it was not influenced by atropine, prostigmine or histamine.

NICOTINE 0.1 to 0.2 cc. of 1:100,000 dilution injected intracutaneously stimulates the arrectores pilorum and gives rise to goose flesh in a 3 to 5 cm. circle within 2 minutes, according to Rothman and Coon. The reaction fails if postganglionic sympathetic fibers have degenerated.

Insensitivity to Pain is a curious and rare congenital abnormality. The girl described by McMurray (ANeurP 64 650 1950) never gave indication of experiencing the sensation of itching and was markedly insensitive to painful stimuli. The female patient of Boyd and Nie (ANeurP 61 402, 1949) likewise did not respond to pain although from time to time she was cut, bruised and infected. She occasionally scratched herself as if she itched and in scratching was liable to produce injuries that ought to have been painful. She sometimes scratched lesions which in normal individuals would have been painful. Arthropathy identical with that of Charcot's joints occurred in a woman congenitally lacking appreciation of pain reported Petrie (JBone&JointSurg 35-B 399 1953). In low grade mental defectives with diseases that ought to have been painful (usten (BMJ 1 1128 1954) observed only indifference; he thought this may be explicable on the basis of defective development of the fronto-ophthalmic projection fibers associated with cortical areas 9, 10 and 12, or defect of these cortical areas themselves.

Chemical Exchange.—EXCRETION comprises (1) fat from sebaceous glands, (2) sweat and (3) exfoliation of epithelial cells, which takes place continuously over the entire surface due to epidermal proliferation.

SEBUM, the sebaceous secretion, is an oily, yellowish, semifluid substance mixed at the sebaceous orifices with dirt, bacteria and frequently *Demodex folliculorum*. Accumulating in quantity on the fetus, sebum forms the vernix caseosa. Under the prepuce, mixed with macerated epidermis, it collects as smegma. Denervation does not affect sebaceous secretion, for sebum is a product of growth.

Hyperhidrosis and seborrhea frequently occur in the same individual but their interrelationship is not understood. Interestingly in seborrhea oleosa of the type not allayed by low fat diet or the administration of thyroid, Banthine or Prantal will temporarily inhibit the outpouring of sebum as well as of sweat.

The mechanism of excretion is intimately concerned with pressure and viscosity for with increasing resistance to further secretion pressure alone stops it (Emmanuel Acta DV 19 1 1938) The capacity of the skin to produce sebum graphs as a straight line if the sebum is constantly removed but the curve shows a decreasing rate of production if the fat is allowed to accumulate according to Zehender and Dunner (Dermatologica 93 3?? 1946) Temperature influences the flow greatly through its influence on viscosity Emotional states excited marked increase of sebum secretion as determined by removing fat and applying osmic acid vapor to detect its reappearance reported Robin and Kepecs (JID 20 373 1953)

Removal of sebum from a given area by means of carbon tetrachloride is followed by rapid replacement which is greatest during the first hour and is complete in about 4 hours (Hodgson-Jones et al.: Acta DV 1032, suppl. 29) When samples were removed from normal women daily there appeared a cyclic pattern related to the menstrual cycle with increase of quantity secreted until about the time of ovulation, this level being maintained until menstruation when there occurred a sharp decline This pattern closely followed that of the rectal temperature

The ether-soluble material of the skin surface shows striking quantitative analogy in distribution of lipids as compared to thermogenic sweat mutual emulsification of lipids and sweat might explain this parallelism (Herrmann et al.: JID 1: 397 1933)

Quantitative chemical analyses of sebum were reported by MacKenna et al. (JID 15: 33, 1950) Free fatty acids comprise about 30% combined fatty acids (glycerides, waxes and other esters) about 30% and unsaponifiable fat about 3?% (hydrocarbo cholesterol, alcohols, squalene, and unidentifiable material) The squalene content of hair fat from boys averaged 1.33% as compared with 5.1% from men and 7.0% from women (Nicolaides and Rothman JID 19: 380, 195?) Analyses of hair fat showed it to be increased in amount during adolescence and diminished in older age (Nicolaides and Rothman: JID 1: 9 1933) Ether-soluble substances on the skins of acneic individual quantitatively exceeded what was found in normal controls and were diminished following x ray therapy but not following ultraviolet light (Prose et al.: JID 19: 227 195?) Vitamins A D and E are absent from sebum (Festenstein and Morton: BiochemJ 5?: 168 195?) The biochemistry of sebum and the physiology of its production were interestingly reviewed in Edit. (BMJ 1: 490 1953)

The fatty acids of sebum are somewhat bactericidal, the unsaturated ones of shorter carbon chain length being most active (Miescher et al. Dermatologica 100 65, 1951)

See sebum as carcinogen (p. 1?16); and under alopecia (p. 1339)

CERUMEN contains a number of free amino acids identified by Bauer et al. (JID 21 205 1953) Anatomy and functions of ceruminous glands were investigated and reviewed by Lobitz and Campbell (JID 19 125 1952) Chemical studies were reported by Akobjanoff et al. (JID 23 43 1954)

APOCRINE SWEAT is discharged in small quantities as a milky fluid. Shelley (JID 17 255 1951) noted that it appears only at the hair follicle openings drying like glue to form a light-colored plastic solid which may fluoresce Its pH resembles that of eccrine sweat. Apocrine sweating may be evoked by stress or stimulated by epinephrine but it does not result from thermal stimulation and is not induced by cholinergic drugs (acetylcholine) or inhibited by anticholinergic drugs (atropine)

The function of the glands seems to be under the control of the autonomic nervous system through adrenergic fibers but inhibitory fibers could not be demonstrated by Shelley and Hurley (JID 20 285 1953) The glands respond to sympathomimetic drugs but not to parasympathomimetic agents. Their response to strong pain or fear stimuli is blocked by local anesthesia. Secretion will appear against an external pressure of 225 mm Hg It could not be produced in children and was reduced in quantity in old people Antiperspirants (e g $AlCl_3$) can diminish or abolish the secretion temporarily

Axillary sweat of two types comes from two different glands (Hurley and Shelley BJD 66 43 1954) the viscid, turbid secretion following epinephrine comes from apocrine glands; the clear watery secretion following acetylcholine comes from near by eccrine sweat glands.

SWEAT is a clear fluid of low specific gravity (1 004) faintly acid, containing mainly sodium chloride some 3 to 40 mg of sugar per 100 cc., and 0.5 gm. of organic nitrogen in the 500 to 3,000 cc. secreted daily It also

contains a little urea uric acid, creatinin, ethereal sulfates and other organic bodies. In uremia chlorides and urea may be deposited in crystals on the skin from dried perspiration. See Barney (J Sc 1373 1925) Loss of vitamins by sweating even if profuse is probably negligible excepting perhaps niacin (Mickelson and Keys JBiolChem 149 479 1943)

The chloride content follows the average skin temperature rather than the rate of sweating (Weiner and Van Heyningen abs YBD 1952, p 391) dietary chloride influences sweat chloride independently of other factors. The acidity appeared due chiefly to the lactic acid content which ranged from 247 to 336 mg % in the normal, higher in males, according to Thurmon and Ottenstein (JID 18 333 1952) The sweat gland is normally a sugar barrier capable of concentrating urea and perhaps able to form ammonia as the kidney does profuse sweat differs from intermittent sweat in that the former contains *no measurable uric acid.*

The normal pH varies in different areas and from single glands, was from 5.2 to 6.8 but not related to the urinary pH. There was no significant correlation between the sodium chloride contents of blood, urine or sweat

There is usually little correlation between sweat composition and disease of the skin, according to Levin et al (UCutRev 44 307 1940) However when ACTH or cortisone is given, the normal mean value of sodium and chlorides is greatly diminished, while patients with untreated Addison s disease show concentrations of sodium and chloride in the sweat far in excess of the highest normal values (Conn AIntM 83 416 1949)

Insensible perspiration consists in water loss from the skin when drops of moisture are not formed on the surface Temperature humidity and air movement greatly influence the rate of water loss. The intact corneum is the main barrier to diffusion. Insensible water loss is increased by from 3 to 10 times in areas of scaly dermatitis (Felsher and Rothman JID 6 271, 1945) There is marked regional variation in the rate of insensible water loss, which is rapid from palms, soles, forehead and cheeks, and slower from the trunk, arms and legs (Burch and Sodeman AmJPhysiol 138 603, 1943 JClinInv 23 37 1944) A film of sweat partially intercepts the erythema producing rays of the sun (Crew and Whittle JPhysiol 93 335 1938)

Secretio is timulated by heat, wind, sun, exertion, anx ty pain, fev pilocarpine, m scarin nt p ret cs Ipecac n cotin, alcohol. It is inhibited by cold, ahydremia, stri gents and tropine Sweat comes from the pores in three ways profuse intermittent and combined, observed Lob t and Osterberg (ADS 56 46 , SIP 5 194 5 69 1945 JID 6 63, 1945 th ir report on ingenious work with single-duct orifices.

If pe h dros was produced b faradic stimulat on of the kin in experiments pe formed by W lk et al. (Brain 61 9 , 1938 who interpreted their results as showing the te f l cal axone reflex overlapping medi ted l y postganglional sympathetics

Sweating nd ced by heating a d that due to mental, emotional or sensory stimuli are entirel und the control f th central nervous ystem, according to Chalmer and Keele (JIJI) 64 42, 193 Whil thermal sweating controlled by the anterior hypothalam c ce ter f temperatu e regulation th cent r controlling me tal weating has not t been ccurate localized. From th central nervou system, descending pathwa s rela around the co nector cells belonging natomicall to the sympathetic system th lat ral h rn f gra matter between the first thorac d seco l l mber segment f th sp l cord These cell ma function independ ntly after severa ce of the cord so t produc prof se sweati g The connector cell in the cord giv rise to preganglional fibe wh h lea th cord vi *the anterior root* d the sympath tic hain. They relay in th mpathet gan_l a, the nerve cell of which rea h the sweat gla ds by way of postgang on fibers tra r g mixed or sensory n rves. Curiou ly wh le sweat gland in rvation f m natomicall part f th sympathet c syst m, the gland respond to drugs a f controlled l th para mpath t c system, being excited by cetyl h l e nd pilocarpi a d h l ted l tropi Volar hyperhidrosis ppea t be caused l hyperactivity *of swat* rath th f d organs.

Histochemic l h ges associated with secretory act vity were i vestigated l y Shelley a d Mescon (JI l 9 19) the only chang i the disappearance of a gl cogen-lik ubstance Th occurs only after intense sweati g and reverses duri g rest. Glycogen depl t on f llo g weating nduced by acet lcholine a metabolic activity f the l m l cell f th weat duct a w ll a of th secretory t bules hi tochemicall *demo trated* l Lol t (Tran ADA 195 That weat gland secrete t m rel filte is evidenced l the f ct th t althou h th rea content of l lood l sweat are parallel, the *sugar* content low in sweat is not.

Absorption by the skin occurs to a considerable degree Abrasion greatly increases the absorptive capacity Iodine sprayed on the skin appears in the urine and saliva in 20 minutes. Mercury is effectually administered by inunctions and vaccines and hormones can be given so Fats with substances dissolved in them absorb largely through the follicular openings (Macht J 110 409 1938 Rothman JLabClinM 28 1305 1943 Mackee et al. JID 6 43 1945) The entrance of water through the skin was proved by Szczesniak et al (Sci 113 293, 1951), using radioactive water

Some gases are absorbed, such as CO_2, NH_3 and H_2S but not CO according to Iburgi (Brux méd 16 1451 1936) Lead poisoning has been known to occur when lead subacetat compresses were used on a patient with exfoliative dermatitis. Bichloride of mercury baths may cause mercurialism in patients with widespread exudative dermatitis. Mercurial inunction results in the absorption of mercury probably from that which has entered the sebaceous follicles (Cole et al.: J 77: 2022, 1941) Methyl salicylate in an ointment can be absorbed through the skin so as to yield urinary excretion level comparable with *those found when aspirin is given by mouth* (Beutner et al.: JLCM 29: 1655, 1943) The incorporation of wetting agents greatly enhances penetrability (Duemling: ADS 43: 264, 1941) Hormones are absorbed percutaneously and produce their physiologic effects (Eller and Wolff: J 114 1503, 2002, 1940)

The penetration of stearic acid into the skin of the rat was interestingly studied by the use of radioactive stearic acid by Butcher (JID 1: 43, 1953) While both the epidermis and dermis acted as barriers, yet radioactive material diffused deeply and widely *throughout the dermal connective tissue the amount of absorption depending on both the* quantity applied and the number of applications.

Intradermal Absorption —When physiologic saline is injected intracutaneously its resorption time, quaddel resorptionszeit (Q.R.Z.) may be interpreted as an index of the state of hydration and the degree of edema. This McClure-Aldrich test was studied with special reference to dermatology by Canizares et al. (JID 13: 323 1949) The disappearance time was fast in exfoliative dermatitis, urticaria and disseminated lupus erythematosus. It was usually fast in bullous dermatoses but was slow in pemphigus foliaceus. Disappearance time less than 55 minutes was considered faster than normal by Hoppe and Christopher (MOO 69 637 1939)

Heat Exchange is accomplished by conduction radiation and evaporation of sweat. This is regulated by nervous activation of the sweat glands and by dilation or constriction of the capillary bed. *Heat loss by evaporation depends* upon humidity and air movement loss by radiation, upon the external temperature and garments. Emotion induces acral cooling by vasoconstriction and hyperhidrosis (Mittelmann and Wolff PsychosomM 1 271 1939 5 211, 1943) The mechanism of heat loss and temperature regulation was discussed by DuBois (AnnIntM 12 389 1938) who emphasized the fact that about *15 kg of tissue is located within 1 cm. of the body surface.*

Temperature.—Investigations of cutaneous temperature are not of great practical importance in dermatology but they have significance in the consideration of vascular diseases. Normal temperature, dependent on environmental and body temperature as well as that of structures immediately underlying ranges usually between 33.5 and 36.9° C Obese persons have lower skin temperatures than thin ones. Symmetric areas have about the same temperature differences exceeding 1° C being scarcely normal The extremities show great variation with environmental changes. If an arm is immersed in hot water the skin of the toes and forehead normally becomes warmer The failure of the toes to warm up under this condition (used as a test) indicates vascular obstruction of some sort. If the arm is immersed in cold water instead of hot, the converse takes place, and failure of pedal temperature response means vascular inadequacy The removal of sympathetic vasoconstrictor influence causes elevation of the temperature of the extremities in vasospastic disease, but not in an occlusive vascular disorder Skin temperature is raised by capillary dilation lowered by constriction. Active hyperemia induced by irritants or inflammation results in increased warmth (Bierman J 106 1158 1936)

Skin temperature seems to diminish with increase in age. Muscular exertion produces a brief fall followed by a considerable rise. There is close relationship of basal metabolic rate and skin temperature. Blushing increases the warmth locally The extremities are more responsive to changes in temperature than are other parts of the body The fore-

contains a little urea uric acid, creatinin ethereal sulfates, and other organic bodies. In uremia chlorides and urea may be deposited in crystals on the skin from dried perspiration. See Barney (J 85 1373 1925) Loss of vitamins by sweating even if profuse is probably negligible excepting perhaps niacin (Mickelson and Keys JBiolChem 149 479 1943)

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Secretion is stimulated by heat, wind, sun, exertion anxiety pain, fever pilocarpine, muscarine antipyretics, peras, nicotin, alcohol. It is inhibited by cold, anhydremia, astringents and atropine Sweat comes from the pores in three ways, profuse intermittent and combined, observed Lobitz and Osterberg (ADS 56 462, 819 827 1947; 57 69 1948; JID 6 63 1943) their report of ingenious work with single-duct orifices.

Hyperhidrosis was produced by faradic stimulation of the skin in experiments performed by Wilkins et al (Brain 61 290, 1938) who interpreted their results as showing the existence of a local axone reflex overlapping mediated by postganglionic sympathetics.

Sweating induced by heating and that due to mental, emotional or sensory stimuli are entirely under the control of the central nervous system, according to Chalmer and Keel (BJD 64 43 1952) While thermal sweating is controlled by the anterior hypothalamic center for temperature regulation the center controlling mental sweating has not as yet been accurately localized. From the central nervous system descending pathways relay through the connector cells belonging anatomically to the sympathetic system in the lateral horn of gray matter between the first thoracic and second lumbar segment of the spinal cord These cells may function independently after severance of the cord so as to produce profuse sweating The connector cells in the cord give rise to preganglionic fibers which leave the cord via the anterior roots and the sympathetic chain. They relay in the sympathetic ganglia, the nerve cells of which reach the sweat glands by way of postganglionic fibers traveling in mixed or sensory nerves Curiously while sweat glands [illegible] form anatomically part of the sympathetic system the glands respond to drugs as if controlled by the parasympathetic system being excited by acetylcholine and pilocarpine and inhibited by atropine Volar hyperhidrosis appears to be caused by hyperactivity of central pathways [illegible]

Histochemical changes associated with secretory activity were investigated by Shelley and Mescon (JID [illegible] 1952) the only change is the disappearance of a glycogen-like substance This occurs only after intense sweating and reverses during rest. Glycogen depletion following sweating induced by acetylcholine is a metabolic activity of the lumen cells of the sweat duct as well as of the secretory tubules histochemically demonstrated by Lobitz (Trans ADA 1953) That sweat glands secrete not merely filter is evidenced by the fact that although the urea content of blood and sweat are parallel, the sugar content is low in sweat [illegible]

for little It would seem that changes in pressure and motion are particularly important in causing particles to enter lymphatics and to move along them and this may occur rapidly and without trauma to the lymphatics. The entry of solutions into the lymph system after their introduction into the skin is rapid Hudack and McMaster (JExpM 55: 431 1932; 56: 223 239 1932; 57: 751 1933) demonstrated

In a dependent extremity the flow stops, McMaster (JExpM 65: 347 373 1937) found while in the horizontal position the flow is slow if the part is allowed to hang and then is raised the flow is brisk the flow stops during venous obstructions and is brisk in reactive hyperemia.

Tissue fluid is thought to be simply a filtrate The normal gradient of blood vascular permeability depends on integrity of the vessel walls and the gradient is unaffected until walls are so damaged as to produce edema Sabin believed that there is a special system of large tissue spaces arising from small spaces by a definite method and possessing a definite structure

The lymph capillaries act like semipermeable membranes in allowing entrance of tissue fluid By the intradermal injection of vital dyes Hudack and McMaster showed that the lymph capillaries consist of a wide anastomotic bed with active flow and that any injury physical or chemical, greatly increases permeability at that site Any injection into the skin is in fact intralymphatic, and so it is almost at once systemic. Retrograde dissemination of dye occurs to a rather surprising degree In cardiac edema the lymph flow is slow and in nephritic edema it is rapid. Cannon and Burt (JImmun 27 173 1934) injected living bacteria into the skin and excised the site as speedily as from 3 to 10 seconds later yet this did not prevent entry of the bacteria into the circulation.

Chemical Composition of the Skin.—The outer layers of the epidermis are composed of keratin, an albuminoid, which Wilkerson (JBiolChem 107 377 1934) found to contain 59% histidine, 2% lysine and 10% arginine There are many different keratins, evidently in various hair feather and horn substances. Human hair and nails contain some 1 % cystine the substance that accounts for most of the sulfur in the skin. The amount of cystine in scleroproteins increases with keratinization while the amount of methionine diminishes (Wilkerson and Tulane JBiolChem 129: 477 1939) In keratinization sulfhydryl is converted to disulfide, the concentration of which is about the same in the Malpighian layer as in the stratum corneum (Van Scott and Flesch: ADS 70: 141, 1954; Montagna et al.: JID 23: 23 1954)

Keratin owes its resistance to dissolving to its disulfide bonds in their original position If split without hydrolysis, the reduced material is keratei e which can be reoxidized to metakeratin (Goddard and Michaelis JBiolChem 106: 60 1934) Keratein and metakeratin were prepared from wool, feathers and human hair by Pillemer et al. (JExpM 69: 191; 70: 387 1939) His serologic investigations indicated that species specificity exists among the k ratins d seem to depend on the redox state of sulfhydryl group gs in the protein molecules. Cornification is evidently a protective mechanism nduced by recession from nutrient and decrease in cell metabolism. It is seen in tissue cultures when transplant tion is reduced in frequency, according to Sil er and Chiego (JID 3: 133, 1940) who gave chemical analyses of keratins, which owe their sulfur content to methionine not cystine they thought and which undergo dissolution with quaternary ammonium hydroxides Analyses f the water-sol bl constituents that may be washed off the corneum were made by Spier et al (DW h 130: 1153, 1954)

The normal state of keratin in hai i the lpha keratin form which has a molecularly folded structure according to Taylo (SciNewsSuppl 93: 8 1941) Beta keratin is the stretched form, and hair can be 'set while in this form, retaining its permanent wave when it slowly reverts to the alpha configuration.

The cid-sol ble pigment of red hair wa identified by Arnow (BiochemJ 33: 1281 1939) Iron-containing it was amed trichosiderin by Flesch and Rothman (JID 6: 257 1945), and ts e traction did not change the color of the hair although the light brown granules of the cortex were removed.

Arseni is absorbed preferentially by keratin, and the presence of arsenic in hair may have i teresting criminologic significance (Smith: BMJ 2: 675 1934) From the medicolegal standpoint arsen may reach the hair from external sources, and merely finding it the ha does not demonstrate its source (Young and Rice: JLabClinM 29: 439 1944)

The water content of the stratum corneum is importantly concerned with the flexibility and comfort of the kin. F ct rs i fluencing this were studied by Blank (JID 21: 259 1953) who found that, a corneum was successively stripped off by means of adhesive plaster the rate of diffusion of wate i to the skin increased little until the base of the corneous layer was reached, whereupon an abrupt increase of diffusion rate was observed.

The major barrier against water loss from the skin is evidently this thin layer. Solvents which remove lipid and alter the corneum decrease the water retaining capacity of the skin and also interfere with the capacity of the epidermis for absorption of water. The result is dehydration of the stratum corneum which becomes brittle. This type of investigation has an important bearing on dermatitis due to defatting agents (q.v.)

The sulfur content of the skin was studied by Klauder and Brown (ADS 31: 26, 1935) who found that scales contain 2.5 times as much as the rest of the skin. The normal sulfur content in nails is 3.-% and is less in some nail diseases; the administration of hydrolyzed wool improved the nail in congenital dystrophy. Sullivan et al. (JBiolChem 119 *1 1937) made the interesting observation that in arthritis the cystine content of the nails is reduced some 15%. Zunz (Eléme ts de Pharmacodynamie speciale Masson, 1932, p. 915) reported that removal of the suprarenal cortex increases the sulfur content of the skin by from -3 to 100%.

Microincineration and spectroscopic studies of the ash of the skin have resulted in interesting findings reported by Kooyman (ADS 32 394 1935) and Gaul and Staud (ADS 29 90, 1933 30 433, 1934). There are found magnesium and calcium, sodium and chlorine sulfur iron aluminum, traces of silicon, arsenic, and copper. Adams (ADS 36 606 1937) observed that in rats, the fat free matter doubles between the 10th and 30th days of life increasing less rapidly thereafter. The water phospholipid, total lipid and oxygen consumption decline with advance in age to a relatively constant value. Quantitative analyses of the metal content of the skin, nails and hair were made spectroscopically and the figures reported by Goldblum et al. (JID *0 13, 1953). Hardness and brittleness of nails are not related to the calcium or phosphorus content (Klie: ADS 0 5, 1954)

The chloride content of the skin tends to be kept in the cells, and its balance is maintained even under adverse conditions. On a diet containing less than 1.0 gm. per day it fell in only 10 of 4 cases did not change in 11 and actually increased i 3 (Volk and Fantl Dermatologica 79 91 1939). Steffanson, the Arctic explorer, has long insisted that adding salt to food is a mere matter of habit, not of necessity and has himself subsisted on a meat diet without added salt for many months.

The nitrogenous material of the normal skin surface comprises amino acids, urea ammonia creatine and uric acid in order of decreasing concentration and is due to insensible sweating (q.v. Rothman et al. JID 13 31 1949). Among the amino acids, arginine and citrulline and perhaps ornithine were identified, along with others, by Rothman and Sullivan (JID 13 319 1949) who thought that urea may be formed in sweat glands from arginine by arginase. Arginase activity is present particularly in the epidermis and its amount is increased in abnormalities associated with epidermal proliferation such as psoriasis and verruca but not in basal cell carcinomas or seborrheic keratoses (Van Scott JID 17 -1 1951). It is to be found especially in the prickle cells, not the basal cells. The urea content of sweat exceeds that of the blood but no arginase activity was demonstrable in fresh human sweat (Van Scott 1951)

The cholesterol and phospholipid content of human epithelium ranges from 13 to 4% and 90% of the cholesterol is uncombined (Eckstein and Wile: JBiolChem 69: 181, 1926). Phospholipid comprises only some 3% of the total lipid. The saponifiable fraction has the same od ne umbe a subcutaneous fat. (See Xanthoma.)

Th derm co ist of white con ective tissue collagen and yellow fibers of elastin. These protei consist of approximately 50% carbon, % hydrogen, 17% nitrogen, and ** % ge w th small amount of sulfur and phosphorus. Elastin co tains some 25% gl ine an l t leuci e co tent of ?1% is ten times as great as that of collagen. Elastin easil digested by pepsin.

The m upol saccharides of pig skin were separated by enzyme hydrolysis and fract nat w th lcoh l in th presence of barium by Meyer and Chaffee (JBiolChem 138: 491 1941 who ide tified hyal ronic acid o e part a d, in the other part hexosamine, cet l ro a l a l sulfuric acid. Watson and Pearce (BJD 59 327 1947) reviewed the b och m try of th connecti e tissues with especial i terest in mucopol saccharides. The muc p t n re combin t on of ca bohydrate w th protein classified mainly by the h ra t ri t c f the carboh drate part. The slimy material extracted from connecti e t ssu w th weak lkal e ntain them. Hyaluro ic acid a d other mucopolysaccharides ha bee fou l n huma kin. The lscou nat re of the ground substa ce of the cutis d subcut eou t ssues wh ch offers resistance to the injection and diff on of foreign subst es l ted to these. The abil ty of an experimental animal to withstand t berc lou fect aries versely with the area of spread of an intracutaneously injected ol t . The M M nus stain normally hows an ntensely colored band of polysaccha les t the dermoep derm l junction *nd alterati l this appearance were* observed mos lermatoses but not in scl roderma by Sto ghton and W lls (JID 14: 37 1950)

Th le t se ontent f normal kin, e cl ding th subcutaneou f t layer, ranges from 60 t l o mg pe hundred grams, according to Cornbleet (ADS 36 1078, 193 ; 41 193, 1940 V lues f glycogen range from 68.1 to 94 mg Dextrose values found in skins of diff r t al rs but the amou t i alwa related to th amou t i the blood. Value f l lood ls greater than those for skin. Superficial l rs of human kin contain m re dext se and glycog than deep ones. Intravenou i jectio of dextrose causes sh rp rise the d t ose co t t of the k but onl little increase in the glycogen cont t. Th de t se curv f r the skin parallel that f the blood with a lag l it rise a l f ll. Subcut eou jection of epi phri i reases the content of d trose

and glycogen in the skin, but changes in dextrose val es are greater and more rapid. Inject on of insulin decreases the dextrose content of skin and increases glycogen. Intra cutaneous injection of histamine increases the dextrose content at that site and changes the glycogen value little Local heating of the skin increases the quantity of dextrose at that site with little change i glycogen content. Cold ultra iolet radiation i creases dextrose in the irradiated skin without affecting that of n nirradiated parts, and the glycogen content is not changed. Three hundred fifty r of unfiltered x ray does not in fluence the dextrose content of skin d ring the following week. A reducing agent chrysarobin, increases the dextrose of the skin on which it is applied but does not change the glycogen content. Dextrose i freely diffusible in skin as well as in other tissues and organ but is not stored in the skin.

Inflammation does not change the normal dextrose content f the skin of the rabbit according to Pillsbury and Kulchar (ADS 30: 459 1934) but after injection of dextrose the inflamed kin may have a higher content. Infection of irritated kin appeared to occur more commonly in rabbit receiving injection of dextrose

The vitamin A in the kin was studied by Cornbleet and Popper (ADS 46: 59 194?) using fluorescence methods. Fluorescence of the skin and appendages is charact ristic the epidermi being dark blue b rati lighter blue-gray basal laye dark, and collagen fibers a trong blue A fading green color of vitamin A was noted in fresh material but the vitamin was located in the fat not in the epidermis, even when high doses had been given.

The quantities of water-soluble vitamin in the skin were carefully measured by Lee et al. (JID 20: 19 1953) who gave figures for the concentrations of B_{12}, folic acid, riboflavin niacin pantothenic acid, biotin thiamine and ascorbic acid. The B group vitamins in hair were found to occur in about the same ratio a in other tissues varying with the diet reported Novak and Bergeim (JBiolChem 155: 283, 1944)

Cholinesterase i present in large amounts in the nerve fibers and about the secretory cel l of the eccrine sweat glands, but not about their ducts or about the apocrine glands, fat glands or hai follicles, or in the epidermis (Hurley et al.: JID 21: 139 1953; Magnus and Thompson (BJD 66: 163, 1954) Preserving enzyme activity by utilizing frozen sections, Findlay (BJD 67: 83 1955) mad biochemical and histochemical studies of the esterases of normal human kin. Cholinesterase and lipase w re not responsible for the hydrolys of the este substrates Findlay used. The cytoplasm of all skin cells howed some measure of esterase activity The high concentrations were seen only along the borders of the epithelia. The peripheral dendritic processes of many connective tissue cells showed some esterase activity

Protease in considerable amount can be extracted from the epidermis (Wells and Babcock JID 1: 459 1933) It is possible that epidermal damage produces dermal inflammation as a result of release of proteolytic enzyme

The location of alkaline phosphatase in the skin interested Fisher a d Glick (PSExpB 66 14, 1947) who reported demonstration of this activity in the stratum granu losum, hairs, hair follicles sweat glands a d endothelium of capillaries, especially in the nuclei thereof The enzyme was present in proliferative fibroblasts of scar tissue and n the cellular infiltrate of acne and eczema.

Pigment is discussed on p. 8. Melanin is formed readily in the protoplasm of oxydase-containing cells of fresh skin when sections a e placed in a solution of 3 4 di h droxyphenylalanine (dopa) The role of coppe in pigmentation ha been investigated. Gorter (Nature 136: 185, 1935) found that pigmentation of the hair f cats and rabbit can be reduced by reducing the intake of copper and increased by increasing t. Copper seems t catalyze the in vitro oxidation of dopa

See also Physiology protection, Anatomy pigment Pigmentation, chemistry and Diabetes of the kin (Hess et al. (Sci 118 414 1953) chemistry of collagen.

Inflammation is a function of living tissues. Various cellular and hu moral responses are physiologic responses to various kinds of insult physical, chemical, or parasitic. Cells have limited capabilities, and the skin can respond in only a limited assortment of ways. Comprehension of inflammation from both gross and microscopic standpoints and a view of it as an activity with a time dimension are fundamental to the understanding of inflammatory disease of the skin as well as of other organs. The student should have gained this from basic science instruction prior to embarking upon dermatology but nowhere else is inflammation more readily observed

Guiding references include Aschoff (Lectures on Pathology Hoeber, 1924), Rich (APath 22 228, 1936) Menkin (JExpM 67 145, 153, 1938 Sci. 101 422, 1945 ib 105 538, 194 Dynamics of Inflam mation, M cmillan, 1940)

The investigations of Sabin and Joyner (JExpM 68 659 837 1938) and many others concerning the histologic responses of the skin to materials injected intracuta eously con stit te the connecting link between discussions of immunity and pathology The inflam m tory reaction inhibits the dissemination of bacteria at that site. Fixation locally is effectual for foreign animal proteins if the body contains specific precipitin for that protein. Fixation is largely dependent on the early outpouring of fibrin, for this precedes the

appearance of cellular inflammatory response; Menkin was [illegible] at the [illegible] localization [illegible] spread of a given bacterium which had been introduced into the skin [illegible] significantly [illegible] inflammation exudation and thrombosis of local lymphatics. An extract from exudate [illegible] serum [illegible] by [illegible] the [illegible] sequences of inflammation by [illegible] the permeability of capillaries causing swelling of the [illegible] the migration [illegible] polymorphonuclear leukocytes. Menkin (II 8) [illegible] that it contains nitrogen [illegible] leukotaxine.

Some inflammatory lesions result [illegible] complete [illegible] or [illegible] fibrosis or atrophy. Pigmentation [illegible] temporarily enhanced or reduced.

Diffusible substances are absorbed from the [illegible] direct entrance into the blood vessels or into the lymphatics [illegible] serum [illegible] subcutaneously appears in the [illegible] duct lymph within 4 minutes but [illegible] the circulating blood for several hours. Inflammation retards the absorption of diffusible substances [illegible] absorption of diffusible [illegible] and dyes, when they have been injected intracutaneously from an inflammatory site than from a normal one.

Immediately after the injection of an irritant [illegible] a rabbit [illegible] a temporary great [illegible] in the resistance of the [illegible] soon followed by a decrease in resistance. When the irritant injected [illegible] turpentine [illegible] streptococci [illegible] the resistance falls to normal with [illegible]. With staphylococci or pneumococci [illegible] normal [illegible] it remains above normal for a week or more with tuberculin. In all [illegible] inflammation, the preliminary period of resistance [illegible] diminished [illegible] appears sooner (Zaders: Jl [illegible] 1[illegible]3).

The Sanarelli-Shwartzman Phenomenon is a hemorrhagic and necrotizing inflammatory response which appears promptly after the intravenous injection of a bacterial filtrate in a site which 24 hours previously was injected intracutaneously with that bacterial filtrate (Shwartzman Phenomenon of Local Tissue Reactivity Hoeber 1937 Sanarelli J 107 18[illegible] 193[illegible] Annin t Pasteur [illegible] 10[illegible] 1939). This type of reaction may perhaps underlie the relationship of focal infection with certain disease processes. ACTH given before *the provocative injection suppressed the phenomenon in 8 of 10 animals* tested (Soffer et al Sci 111 303 1950). Nitrogen mustard also completely suppressed the effect (Race and Reed SouthMJ 4[illegible] 207 1953). A fatality induced by antibiotic therapy was attributed to the Shwartzman reaction by Nelson and Braslow (ADS 68 728 1953). The significance of the phenomenon in the etiology of dermatoses with reference to purpura gangrene leprosy and acute pemphigus, was discussed by Rostenberg (JID [illegible] 789 1953).

Such inflammation was described from the standpoint of histopathology by Stern (APath [illegible] 41 1938) and [illegible] Stetson (JExpM 93: 4[illegible] 1951). Swelling at the site [illegible] to necrosis. There are [illegible] polymorphonuclear cells [illegible] of the [illegible] with serous and fibrinous [illegible] red blood cells [illegible] Small [illegible] capillaries are plugged by leukocytes and platelet thrombi [illegible] found in lymph nodes as well [illegible]. Polymorphonuclear and mononuclear leukocytes encircle the vessels and penetrate the wall. In the [illegible] the cellular infiltrate resembles granuloma. Increased capillary permeability allows the outpouring of fibrinogen, the deposition of fibrin, and *the thrombotic localization [illegible]*.

Immunology.—The skin is an important organ from the standpoint of immunity. The breadth of its function is indicated by the fact that a great variety of antigenic substances inoculated intracutaneously evoke responses which are characteristic and useful for diagnostic purposes. Among such tests are those for tuberculosis, chancroid, Brucella infection, trichophytosis, moniliasis, echinococcosis and venereal lymphogranuloma. Extensive lists with bibliography are given by Sutton and Sutton (Diseases of the Skin, Mosby 1939 p. [illegible]) and by Baer and Yanowitz (ADS 6[illegible] 491 1950). For a careful discussion of the values and dangers of intradermal tests, see Beerman and Ingraham (AmJMSc 220 415 1950). Percutaneous immunization is possible. Intracutaneous immunization requires comparatively little antigen.

Specifically Altered Reactivity (Allergy) of the skin is closely interrelated with immunity. From a broad standpoint an allergic reaction is an ineffectual and distorted immunologic one. Allergic reactions comprise not only specifically acquired hyper-reactivity (hyperergy) but also specifically

acquired hyporeactivity (hypoergy) and specifically acquired immunity (anergy) Excessive reactivity of the skin varies as to degree. In a given skin, reactivity may fluctuate with nervous, emotional or physiologic activity An allergic response depends on reaction of the noxious substance (allergen) with the susceptible skin immediately in the form of solid liquid dust or gas, or mediately by way of the blood (Sulzberger et al J 104 1489 1935 YBD 1943 p 7 1944 p 7 1945 p 7) Newer concepts of allergy to drugs and bacteria were interestingly set forth by Lowell (J 136 665 1948) Allergy seems to explain a great deal but allergy itself is difficult to explain

See Duke (Allergy Asthma, Hay Fever, Urticaria and Allied Manifestations of Reaction, Mosby, 1925); Sulzberger et al (J 104: 1489 1935); Sulzberger and Goodman (Mitre 143 17 1936) Sulzberger (JAllergy 7: 308, 1936); Sulzberger (Dermatologic Allergy Thomas, 1940); Urbach and Gottlieb (Allergy Grune & Stratton, 1944); Sulzberger Baer et al (Office Immunology Including Allergy Year Book Publishers, 194); Raffel (Immunity Hypersensitivity Serology Appleton-Century-Crofts, 1953, p. 631)

Alteration of reactivity does not denote allergy unless the alteration is specific A skin irritated by a caustic, for example, manifests sensitivity to mercuric chloride but not specific hypersensitivity; a skin manifesting contact dermatitis, whatever the cause usually manifests excessive irritability to soap and its erythema is intensified by warmth but these are not allergic reactions

Von Pirquet and Schick (Die Serum Krankheiten Leipzig 1905) found that an animal after responding to a first injection with a foreign serum reacts differently to a second injection of the same protein. There was needed a lapse of time an interval of a week or more for development of the change and this period of some 8 to 13 days corresponds to the incubation period of many infectious disorders. For altered reactivity they suggested the term allergy One dose of horse serum provokes hypersensitivity in the guinea pig but repeated tolerated doses induce immunity reported Weil (JMRes 27 497 1913) and the serum of the immunized animal will induce hypersensitivity in a normal one Weil indicated thus that the same antibodies are present in allergy as in immunity but in the former their location is predominately in the cells, and in the latter in the serum The immunized animal is potentially anaphylactic, his cells possessing anchored immune bodies, but he is protected by immune bodies in his circulation. Allergic reaction apparently is due to reaction between specific antibodies in cells with the introduced antigen. In immunity on the other hand antibodies present in the serum neutralize introduced antigen and so protect body cells

It is believed that as a result of antigen-antibody reaction, stored up vasodilator substances are set free from the fixed tissue cells, and these freed histamine-like substances are the immediate cause of the typical allergic reaction (Dale and Laidlaw: JPhys 52: 355 1919) It may be that histamine is actually the noxa so released for histaminase is said to diminish allergic reactivity and injections of histamine may induce refractoriness to histamine and diminution (but not disappearance) of allergic reactivity (Edit J 115 1023 1940) Benadryl relieves serum sickness (Peterson and Bishop J 133 1277 1947) and antihistamine drugs are effectively palliative in urticaria hay fever and asthma presumably by virtue of their ability to nullify histamine

Anaphylactic shock has long been attributed in the main to products of proteolytic digestion in the blood plasma. When serum is rubbed up with agar starch or kaolin it becomes anaphylotoxic. Dale s experiments, according to an Editorial (BMJ 1 807 1952) indicated that histamine was released and that anaphylactoid phenomena seemed explicable on the basis of production by these agents of tiny emboli composed largely of platelets and leukocytes. If the isolated liver of a sensitized dog is perfused with a fluid containing all the blood cells histamine and heparin are released in large amounts and the release of histamine is accompanied by the formation and disintegration of microthrombi of platelets and leukocytes in the liver capillaries. The amount of histamine released greatly exceeds, however t amount available from the cells that disintegrate. Likewise when seru

cubated with agar is perfused through guinea pig lungs again much histamine is released Rocha e Silva et al (BMJ 1 702 1952) showed that 4% isotonic trisodium citrate in water appeared to protect the platelets from disintegration and to prevent the development of anaphylatoxic properties in the serum so that it had therapeutic value

Allergy to tannic acid a non-nitrogenous simple naturally occurring compound was observed in a patient whose scratch test was of the immediate urticarial type and whose reactivity was passively transferable by Johnston et al (J Allergy 22 494 1951)

A ph logenetl concept of all rgy wa presented l William (PSMJC 8ts 518 1949) who review l tri ll th hi t rical es lution of th ul ject Ehrli h (Dmed W hn 1 9 0 1891) and von Pirquet (Mun h med W hn 53: 113 1906) conceived all rgy a a harmful type f dev lopment of immun l lie in contradi tinction to the view of cellular immunity propounded by Metschnik ff (Ann path Inst 9 1 o0 1 4) Kahn (Tl ue Immunit Th ma 1936) d nied any fund m ntal differen e in ph i logic mech ani m of immunit and allergy l fining th all rgi i divid l a on who mor vio lentl than th normal rea t t a gi n qu ntity of antigen and who develops immunity m r readily Two main cla ses f allergy exi t th t with circulating antibodies and that without Perhaps two k nd of gamma globulin xi t in xplanation of thi one being s luble di solved in th blood tream and respon ibl for circulating antibodies and a being insolubl fixed in th cell and respon ibl for granulomatou inflammation. In th pathogen i of alle gic lesion necrosi of th collag n fibrils i the earli est observable path logi hange Some microorganism are prod tive f mu h exotoxin th coci especially resulting in apparatl inflammation and abundant circulati g anti bodies wh l oth rs pecall tr pon mata and ca t are poor producers f x toxin and adu ce granulomat inflammation ften with enough circulati g antibod produc t n t g v rise to spec fi k n s s is it In ph i al all g h contra t no antigen ant bod mechani m i present ascular injury a d th t p cal lin cal p tur be ng prod ed l y an x a. Yet these three types f allergy are l no means necessarily mutu all x lu an l in ma l nical ase tw or n three types f alle gy ma coexist

Th nfl ce f ac t infect on n all rgy oncerned F ingold (J ed 34 515 1949) wh bserved in allergi hildren aggravation of th mptom of allergy d ring the period of in u t prod omal tages of certain illnesses and d ring the height of the inv on rather than the early tag of re t in other illnesses A the infect on sub ded, th symptom f alle gy spontaneou l improved. The fi t patt rn wa produced gen rall l those fection which conf permanent immunity an l r associated with leuk penia wh le th second patt n wa prod ced l y infection which call f rth leuko tosi and conf r n mmunit Bi k and Callaway (AIM 59 9 0, 1937) w re in t rested the fact that a ou f rm od pe tula dermatoses flar up an l becom i ght sen t pe haps d ring adven n and oth r d l il tat ng int rcurrent d seases, pos ibl ber use of gen ral low ring of th threshol l f re ct on t damage

All gy to food ha been known a ca se f abdom nal pain and ga trointestinal mpt ms t ca a d rmatit migrain and l on hial asthma. It affects adults a well a hi l It t a common a facto d rmatoses as most persons imagine

Corr lat on f uscept bility t lle gy a d emotional and ps chiatric a pect of the d ea l h e r ei consideration a d it i thought b some that the "allergic personal t m t (Stokes and Beerman P s hosom M 1 438 1940)

H perse sit t n cold blooded a m l was reviewed a l investigated by King and Ore (Bei 100 565 1949) Anaph lax ha been demon trated in several teleost species.

Histologic changes are correlated with immuno-allergic processes When local reaction rapidly destroys attenuates or otherwise renders innocuous microorganisms or their products tuberculoid structure usually is found (Jadassohn-Lewandowsky law) Tuberculoid structure is not seen as a response to drug allergy

Configuration of lesions grossly is also frequently correlated with immuno-allergic processes. When a zone of absolute or relative specific resistance develops peripherally the local process may assume a corymbiform shape for satellite lesions are impeded in their growth Central healing results in annular shaping for the healed zone manifests increased immunity (cf Koebner phenomenon) while the spreading margin manifests activity While disease processes are often explained by immuno-allergic theory explanation of the explanation leaves a good deal to be desired Compare these arguments (1) annular shape results from development of immunity in the cen

tral part of the lesion so that the central part heals and (2) the central part has healed so that immunity may be assumed to have developed there Some investigators appear to see from within outward.

THE ARTHUS PHENOMENON is characterized by the provocation of progressive infiltration induration edema and aseptic gangrene in a site by repeated injection of a foreign protein Such anaphylactic gangrene has followed the repetition of injections of antisera into human beings (Tumpeer et al J 96 1772, 1931 Irish and Reynolds: J 100 490 1933)

SENSITIZATION OR CONTACT TYPE, which is without circulating antibodies, is the basis of a large proportion of dermatologic practice Sensitization may be provoked by the most diverse substances see p 118 ff

SKIN TESTS are discussed with Dermatitis venenata (q v) A positive skin reaction to an allergen reveals a person with allergies (positive reactor) who may or may not have active clinical allergic symptoms, wrote Peshkin (J 157 820 1955) all forms of testing are best regarded as furnishing confirmatory rather than final evidence Skin testing with food antigens especially is of restricted value and in children elimination of foods from the diet solely on the basis of skin tests may seriously interfere with nutrition and at the same time not help the allergy (Edit J 157 825 1955)

FOOD TESTING —Mistaken confidence in food tests has resulted in erroneous interpretation of dermatoses which were actually due to malnutrition infection and contactants food allergies are in fact not common I agree with Babalian (Maine MAJ 39 194 1948) Skin tests with foods, regardless of the type of material used and the method of testing yielded results not over 40% accurate in the extended experiences of Rinkel (JMoSMA 40 91 1949) Skin testing with a food extract killed a patient of Swineford (J Allergy 17 24 1946)

Hyposensitization is a state of partial protection which is induced by small repeated doses of an allergen Hardening occurs in perhaps 90% of industrial employees who handle irritating chemicals (such as TNT) an ability to withstand further contact without irritation a fact which Schwartz taught skeptical dermatologists. Abstinence from contact with the sensitizer may be followed in a few months by loss of this immunity The case usually seen by the dermatologist is the one who is unable to develop hardening Schwartz (ADS 42 318 1940) pointed out

The therapeutic establishment of an antianaphylactic state is not often satisfactory in dermatology It is better to discover the offending material if possible and to segregate the patient from it In practice segregation can generally be accomplished without identifying the allergen positively see Dermatitis venenata treatment

Deallergization (Urbach JID 3: 493, 1940) may be attempted in various ways and it may be partial or total and temporary or permanent. Generally it is sought by repeated administration of minute doses of the antigen such that no gross reaction takes place If an overdose induces macroshock, and if the animal survives, it is deallergized for life Urbach coined the word keptophylaxis for the procedure of giving little doses intended to consume the tissue antibodies and he thought it worked best when attempted orally Hyposensitization in the contactant type of allergy is, for all practical purposes, a failure—it does not work. It is difficult to convince the medical public of this fact, for there is great popular faith in, for example, poison ivy shots. Regarding palliation of allergic symptoms by means of drugs, see Treatment Antihistamines, and Cortisone and ACTH.

Classification of Allergic Phenomena.—Sulzberger and Goodman (MRec 143 17 1936) defined allergy as an altered state of reactivity by a first contact and made manifest by subsequent specific contacts. The term allergy must therefore include acquired hypersensitivity hyposensitivity and absence of sensitivity all probably due to closely related mechanisms.

I. **Anaphylaxis**—occurs in laboratory animals is specific is linked with particular phenomenon is associated with antibodies which occur with (and may be identical with) precipitins

the bronchioles, and the vascular apparatus of the superficial cutis. The reactions of the contact form of allergy are located primarily in the epidermis. The skin is frequently implicated in many different forms of allergy but no organ is immune. The commoner forms of allergic response include

Localized Reactions

HEMATOLOGIC SYSTEM: bone marrow lymphatic system, perhaps the blood cells themselves, agranulocytosis; thrombocytopenic purpura, etc., eosinophilia.

EYES: especially iri conjunctiva, lens; iritis; vernal catarrh, etc.; cataract in atopic dermatitis.

NOSE AND SINUSES: rhinitis, acute and chronic sinusitis, polyps

BRONCHI AND LUNGS: asthma; other acute and chronic infectious and noninfectious processes.

SKIN: contact dermatitis urticaria and angioneurotic edema, atopic dermatitis miscellaneous dermatological manifestations, such as generalized r localized erythemas, erythema nodosum and erythema multiforme; drug eruptions (acneiform, furunculoid, fixed purpuric); and infectious exanthemas, such a in syphilis, leprosy and the exanthemas f childhood.

GASTROINTESTINAL TRACT: various types of acute or chronic, spastic, or inflammatory reaction.

LIVER: acute yellow atrophy arsphenamine jaundice, et

GENITOURINARY TRACT: cystitis (?) nephritis (?)

JOINTS: arthritis, intermittent hydrarthrosis.

CENTRAL NERVOUS SYSTEM: migraine epileptiform seizures, asthenia, psychic disturbances (especially in children) neuralgia, transient paralysis and nerve dysfunction (?) and perhaps some organic diseases, such as multiple sclerosis.

CARDIOVASCULAR SYSTEM: hypertension (?) hypotension (the rule) cardiac irregularities tachycardias, extrasystoles bradycardias, precordial pain. Buerger s disease (?) migratory phlebitis (?) periarteritis nodosa (?)

Generalized Reactions

ALLERGIC SHOCK: subnormal temperature, slow pulse lowered blood pressure prolonged coagulation time, increased N P N decreased blood chlorides, decreased blood calcium and phosphorus, decreased sugar tolerance leukopenia.

SYMPTOMATOLOGY AND PATHOLOGY

Dermatologists are not strict rhetoricians in the differentiation of symptom and sign. Dermatoses are brought to them by their patient because of itching more commonly than for any other single complaint. Itching, burning, tension, dryness, cracking, crawling, tingling, soreness, pain, numbness are words used by the sufferer. He may feel a bump or roughness or describe his sores or blisters or complain of unsightliness. He may be heeding the excellent advice nowadays well publicized to attend to a small matter even though asymptomatic because its consequences lie not within his knowledge.

Objectively, external manifestations in cutaneous medicine are composite pictures resulting from the conjoint development of various elementary lesions. These essential primary eruptive elements are relatively few and simple. As a result of the continued action of a pathologic process, secondary infection or trauma, primary lesions may undergo various modifications and so be transformed into consecutive or secondary lesions. The following definitions of gross and microscopic lesions afford a basic vocabulary for description of what is to be seen. But they are not sufficient for the dermatologist is obliged to a l l numerous adjectives concerned generally with color, texture, distribution, temperature and even odor in order to describe with some accuracy and completeness. His finger tips help a dermatologist greatly and his nose not a little.

Gross Lesions.—Each has an underlying histologic basis, and the student must constantly strive to interpret from visible processes their microscopic make-up. The microscope is only an adjunct to the eye. It does not introduce a new world. Any lesion is a manifestation possessing three dimensions in space and a fourth in time and yet another in the psychologic and sociologic relationships of an individual.

PRIMARY GROSS LESIONS

Macules are circumscribed discolorations of the skin which are neither elevated nor depressed.

Papules are small variously shaped circumscribed solid elevations.

Wheals are rounded, elongated or irregularly shaped edematous, transitory elevations of which hives are typical examples.

Nodules are circumscribed solid masses which may lie above, level with or beneath the surface. Tubercles are nodules of bean- to pea-size, firm and deeply seated. Tumors are variously shaped lumps of relatively large size.

Vesicles are circumscribed pinpoint to pea-sized elevations containing free serous fluid. Blebs, or bullae, are vesicles of large size. The burrows of scabies are linear mite-made vesicles, overlying secondary inflammation.

Pustules are circumscribed elevations containing free purulent fluid.

Telangiectases are tiny red linear lesions due to the presence of dilated capillaries.

SECONDARY GROSS LESIONS

Excoriations are superficial traumatic discontinuities of the skin.

Fissures are linear breaches of continuity generally sharply defined with abrupt walls and inflamed bases.

Scales are dry or greasy laminated masses of superabundant epidermis. They range in size from minute furfuraceous fragments to large sheets of horny material.

Crusts are masses of dried exudate

Ulcers are irregularly sized and shaped excavations of the integument due to injury or disease Connective tissue is lost and healing results in scar

Scars, or **Cicatrices**, are connective tissue new formations which replace loss in substance in the fibrous layer of the skin.

Microscopic Lesions are the basic morphologic changes upon which rest the gross evidences of disturbance They may be cellular, intercellular humoral or mixed. Inflammation (q v) is discussed as a physiologic process. Histologic descriptions of diseases are found throughout the text

CHANGES IN THE EPIDERMIS

Hyperkeratosis is hypertrophy of the horny layer as in callusea. Nuclei are not visible in the keratin mass.

Parakeratosis is retention of nuclei in the cells of the horny layer due to defective keratinization.

Acanthosis is thickening of the stratum germinativum due to increased mitosis in the rete cells.

Inclusion bodies are intracellular bodies, such as are seen in Darier s disease highly anaplastic carcinomas, and virus diseases, such as herpes, molluscum contagiosum and variola.

Atrophy consists in general thinning of the epidermis with diminution in the accessory epidermal structures and flattening of the papillae It is usually due to defective nutrition from the corium, or to stretching over an enlarging dermal mass.

Edema, when intercellular spongiosis, is shown by widening of inter cellular spaces. If the severity is such as to rupture the intercellular bridges, the result is an intraepidermal vesicle Intracellular edema takes several forms. In reticulierende collaquation, vacuoles develop in the protoplasm of several cells, the nuclei degenerate, the cells swell to bursting and multilocular vesicles are formed. In ballonierte degeneration, ' young epithelial cells balloon up and become loosened one from another so forming a vesicle In alteration cavitaire, the protoplasm becomes homogeneous and stainless, and perinuclear edema appears, which may increase till the cell ruptures, a third method of intraepidermal vesicle formation

Neoplastic proliferation occurs from the epidermis (basal-cell and squamous-cell carcinoma) and from the epithelium of accessory structures (epithelioma adenoides cysticum) Malignancy is indicated by profusion of mitoses, metaplasia of the cells, invasion beyond a basal membrane and abnormal position of active epithelium.

Pseudoepitheliomatous hyperplasia exists when the normal epidermis is notably hyperabundant, as it may be in response to granulomatous inflammation of dermal papillae or at the edges of chronic ulcers.

CHANGES IN THE DERMIS

Fibrous tissue may be hypertrophic (keloid elephantiasis) or atrophic (old irradiation scars, senility) It may undergo colloid change as in hyalinization of old scars, or mucoid change as in x ray dermatitis. Amyloid deposits may occur about the capillary loops. Lipids of various kinds may be deposited intracellularly or intercellularly or both. In rare instances calcification is found. Degenerate collagenous tissue which stains like normal elastic tissue is called collastin Burns, caustics, powerfully toxic substances, and vascular occlusion are causes of necrosis.

Elastic tissue may be overabundant, as in cutis hyperelastica, or defective, as in epidermolysis bullosa. Elastic fibers that become thick, swollen, broken up and abnormal in staining properties, form what is called collacin.

Infiltrations with various cell types may be localized, perivascular and perifollicular or massive They consist of various proportions of polymorphonu-



Fig. 43.—Parak[illegible]ratosi[illegible] a[illegible] [illegible]athosis, i[illegible] [illegible]xfoliati[illegible] dermatiti[illegible] (Dr. H. Pi[illegible]kus.)



Fig. 44.—P[illegible]rak[illegible]ratos[illegible] i[illegible] tw[illegible] different forms, in seborrheic d[illegible]rmatitis. (Dr. H. Pink[illegible].)



Fig. 45.—Spongif[illegible]rm epithelial [illegible]bscess, i[illegible] [illegible]cute psoriasis. (Dr. H. Pinkus.)

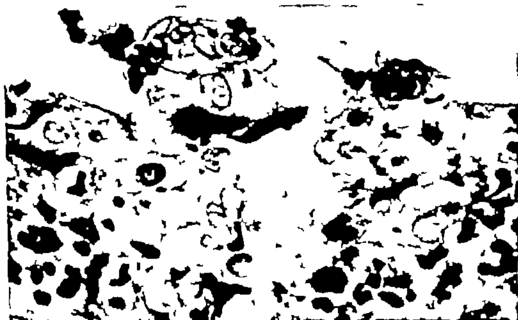


Fig. 46.—Intranuclear inclusion bodies, in herpes simplex. (Dr H. Pinkus.)

Fig. 47.—Cytoplasmic inclusion bodies in molluscum contagiosum. Near the bottom of the picture is the dermo-epidermal junction. (Dr H. Pinkus.)



Fig. 48.—Carcinomatous dyskeratosis [illegible] Bowen's disease. (Dr. H. Pinkus.)

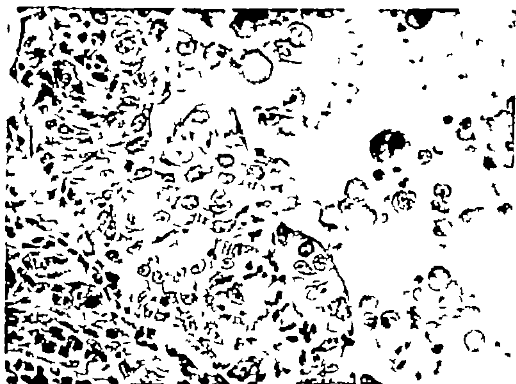


Fig. 49.—Keratinization of individual epithelial cells in a squamous cell carcinoma of slight cohesi[illegible]. (Dr. H. Pink[illegible])

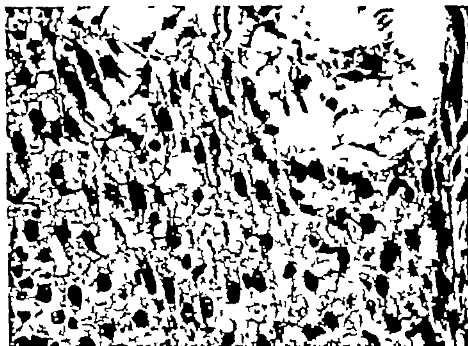


Fig. 50.—Spongiosis and vesiculation due to intercellular edema, in dermatitis venenata. (Dr H. Pinkus.)



Fig 51.—Disintegration of basal layer of epidermis, in discoid lupus erythematosus. (Dr H. Pinkus.)



Fig. [illegible].—[illegible]epidermal bulla formation, in erythema multiforme (Dr H. Pinkus)



Fig. 11.—Subepidermal bulla formation, in dermatitis herpetiformis (Dr H. Pinkus)

Fig [illegible].—Acantholysis. Early bulla formation by epithelial cell degeneration, in pemphigus of familial benign type (Dr H Pinkus.)



Fig. [illegible].—Reticulated degeneration of epidermis, in herpes simplex (Dr H Pinkus.)

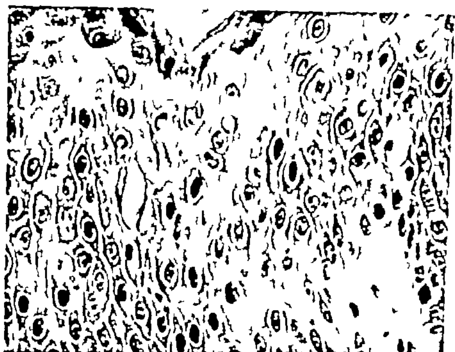


Fig 66 —Alteration cavitaire form of epithelial degeneration leading to vesiculation, in pemphigus (Dr H Pinkus)

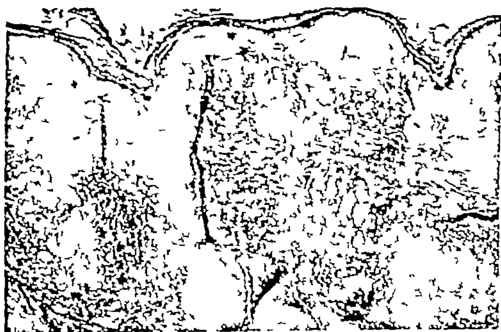


Fig 67 —Pseudoepitheliomatous hyperplasia, in discoid lupus erythematosus of the lip (Dr H Pinkus)



Fig. 58.—Hyperkeratosis and follicular plugging, with atrophy and degeneration of the papillary layer of the dermis, in lichen sclerosus et atrophicus. (Dr H. Pinkus)



Fig. 59.—Subepidermal melanotic hyperpigmentation, in "symptomatic incontinentia pigmenti" secondary to subacute lupus erythematosus in Negro. (Dr H. Pinkus.)



Fig. 60.—Perivascular lymphocytic infiltration, in seborrheic dermatitis (Dr H. Pinkus)



Fig 41 —Phlegmonous inflammation of the dermis with infiltration by mostly polymorphonuclear leukocytes, in leg ulcer biopsy (Dr H. Pinkus)



Fig 42.—Epithelioid and giant cell infiltration due to paraffin put into the skin (Dr H Pinkus)

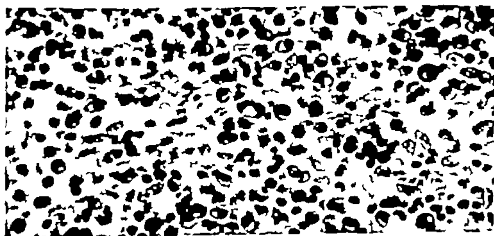


Fig. 43.—Plasma cell infiltration of chronic inflammation in granuloma associated with sebaceous cyst. Note binucleated plasma cell near center (Dr H Pinkus.)

clear leukocytes, lymphocytes, mast cells, plasma cells, and cells of reticulo-endothelial origin including giant cells. Histiocytes are cells capable of ingesting foreign substances. The infiltration may be circumscribed or limited to relationship with certain structures or it may form a massive cell infiltrate without reference to vessels or glands. With inflammatory infiltration are associated fibroblastic and endothelial proliferation. Acute processes are characterized by numbers of polymorphonuclear leukocytes; more chronic ones have higher proportions of lymphocytes, eosinophils, and plasma cells. Neoplastic cell infiltrations occur.

Vascular changes consist of vasodilation as in mild sunburn, edema wherein fibers are further separated than is normal and may take a foggy stain, hemorrhage by rupture as in trauma, or by diapedesis as in purpura, inflammation, and thrombosis or occlusion, partial or complete, as in peripheral vascular disease with gangrene (q v). Necrosis occurs in new growths which outrun their vascular supply, as in gummas or caseating tubercles.



Fig. 14—Necrobiosis of dermis with palisade arrangement of histiocytes, in granuloma annulare. (Dr H. Pinkus.)

Pigment occurs in chronic inflammatory conditions as an oversupply of melanin. It occurs abnormally as hemosiderin after hemorrhage into the skin. It is produced abnormally in large quantity as melanin in both benign and malignant neoplasms. Pigment of extrinsic origin occurs in tattoo.

Neoplastic changes in the dermis may affect any structural element there present. Hemangioma, lymphangioma, fibroma, neuroma, myoma, even osteoma, are found, along with sarcomas of various kinds, primary or metastatic.

References on Pathology. Unna (Histopathology of Diseases of the Skin, Walker transl., Macmillan, 1896); Gans (Histologie der Hautkrankheiten, Springer, 1925, 1931); McCarthy (Histopathology of Skin Diseases, Mosby, 1931); Wells (J 114: 2177, 2294, 1940), adipose tissue; Wiser (ADS 42: 658, 1940), pseudoepitheliomatous hyperplasia; Hass and McDonald (AmJPath 16: 525, 549, 1940), production of collagen and fibroblasts; Cornbleet

Fig 43 Senile [illegible] tosis, [illegible] ad Giemsa staining in tissue from the lower lip. (Dr H Pinkus)



Fig. 44—Elasti tissue degeneration in the subpapillary portion of the dermis, in pseudo xanthoma elasticum (Dr H. Pinkus.)

(JID 4 481, 1941) vesiculation and the Donnan equilibrium; Arnold (ADS 48 268, 1943) staining reactions of skin tissues; I ans et al. (Anat Rec 86; 545, 1943), aging changes; Passeber (Jimmunol 46; 195, 1943) the tuberculoid reaction; Ib khart and Montgomery (ADS 49; 19, 1944) eosinophiles; Dublin (ADS 5 ; 461 1944) tal ing technic showing melanin, epithelium, nuclei, nerv 19 ko (ADS 49, 255, 1944) acid orcein-Giemsa staining technic and interpretations; Ma Lond and Mu mle (Practic l Handbook of the Pathology of the Skin, Lewis, 1946); Perci l t L (Atl f Histop thology of the Skin 14 Livestone 1947) Ehrlich (J 125 94 1947) tissue reactions t tissue W y (ADS 56 178, 1947) reticulum fibers; Montgomery et l. (Atlas of Derm t l thology Registry Press, 1948) Percival nd Hannay (BJD 61 4, 77, 1949), bulla formation 10 nk (JID 12, 92, 1949) rapid embedding technic Lalit (J 14 ; 87) 1950) plasma cells Wiener and Lipschultz (ADS 65; 270 1952) cytology of vesiculating eruptions Ca o (ADS 67 18, 1953) dermal patholo gy in diagnosis Somme ville (ActaD-V 33 48, 1953) pseudoepitheliomatous hyperplasia; Oli er (ISMJ 1 511 1954) technics useful in dermatologic diagnosi White head (ISMJ 1 1284 1954) the biopsy; Haber (BJD 66, 79 1954) cytodiagnosis Hille et al. (JID 2, 199, 1954) capillary microscopy Lever (Histopathology of the Skin, ed. 2, Lippincott, 1954) Pinkus (AnnAllergy 12; 671 1954) histopathology of allergic dermat ses, illustrating tissue hanges dependent on epidermal, urticarial and tuberculoid r ponses Lisbon (SouthMJ 48 21 1955) utility of histol gic studies in clinical medicine ex mples.

ETIOLOGY

Etiology is derived from the Greek for "discourse upon causes" and is defined as "the sum of knowledge concerning causes." One must be very wise to know much about causes, for things which might be called simple turn out not to be when scrutinized. As a physician's age and experience increase and his comprehension of the individual problems he meets in his daily work becomes more detailed, his sense of insecurity becomes greater regarding the ultimate knowledge of the nature of causation and its relation to time, for sequence is an inherent part of cause and effect, and to happenstance, for a phenomenon has its unique four dimensions of space and instant. So we can talk longer about a given phenomenon but seem to ourselves to be less on the point and rather to be merely in its vicinity. The cut finger of the housewife whose paring knife slipped becomes not merely a proposition of sharp steel, yielding flesh and physical dynamics but takes on in addition the contributing relationships of whether the woman felt well, slept well, hastened because of social commitments, was angry with her husband or preoccupied with thoughts of the illness of her child. Were her hands slippery with detergent, or her fingers cold and clumsy because the furnace failed to operate correctly—and if it didn't, why didn't it? Was the tool ill designed for its intended use? Why did she not plan something for that meal other than something that had to be pared? The restless mind pursuing the endless ramifications of the "simple" trauma finds itself flustered and dissatisfied even though its sum of knowledge regarding causes is richer than a superficial and naive estimate of the event.

Etiology and diagnosis are inseparably interrelated. To diagnose, or "see through," one must comprehend the intricacies of the background. On the other hand, if one possessed full comprehension of the etiologic background, one would certainly "see through" in the diagnostic sense. An old dermatologist, if he were not too old, could lecture for an hour without preparation or reference to notes on any one of the succeeding sentences of this brief chapter.

In the skin the changes that take place as a result of disease follow the same laws that apply to changes in other parts of the body. Damage may be sustained directly or indirectly. Indirect damage may be mediated by the *blood vascular, lymph vascular or nervous system. Many disorders of the skin are secondary to some derangement of the internal economy.* Others originate in the skin itself and confine their action to this organ alone. The skin is exposed to injurious agencies as other organs are not. *Combinations* of factors are frequently at work in any given patient, so that a dermatologist must daily unravel problems which necessitate a multiplicity of simultaneous diagnoses, a multiplicity astonishing to monodiagnostic purists. For example an age-sex-occupation predisposition in combination with a trauma-medicinal-parasite excitation may explain a secondarily infected, medicinally irritated hangnail on the finger of a stenographer whose digits would not have been rough if she did not scrub off carbon, and who developed sensitivity to the phenol-sulfonamide component of nail lacquer when she scratched her pruritic disease and who got a generalized severe eruption when the infection was treated with a sulfonamide by mouth.

Predisposing Causes.—*Age.*—Some diseases of the skin usually develop only at certain periods of life, while others may appear at any time. Ichthyosis, angioma, epidermolysis bullosa and congenital syphilis appear in infancy. *Children are particularly susceptible to the parasitic diseases*, such as impetigo, tinea capitis, and favus. Acne vulgaris and psoriasis usually start in early adult life. Pruritus and carcinoma are diseases usually of an older age.

See Lynch (ADS 6 957 193) dermatoses of fetus; Dixon (CanadMAJ 39: 261, 1938) childhood dermatoses; Hill and Montgomery (JID 3 31 1940) histology of aging changes; Mintzer (ADS 4 4 3, 1940) dermatoses in girls; Brunsting (TexasSJM 37: 32, 1941) childhood dermatoses; Mackee and Cipollaro (Skin Diseases in Children, Hoeber 1946, 440 pp. 220 ill. s., bibliography); Ormsby (J 138 431, 1947) dermatologic geriatrics; Strobel (AfDuS 186 676, 1948) disease hazards during aging; Lane and Rockwood (NEnglJM 241: 772, 1949) geriatric dermatoses; Kennedy et al. (SouthMJ 43: 128, 1950) skin dermatoses.

Sex is a factor in the etiology of many cutaneous disorders, not only hormones but also habits being concerned.

See Severinghaus (ADS 43 63, 1941) endocrine dermatoses; Lynch (Min M 23: 629 1940) endocrine (Lller and Kest NYSJM 40 182, 1940) endocrine Dunlop (BJD 63 43, 1951) hormones and dermatoses; Wy and Andrews (ADS 61 578, 1950) hormone therapy.

Race and Nationality.—The proclivity of the Negro to keloid, for example is well known (Lewis: PIM(Chi 1 : 11, 1919). Skin cancer is unusual in the Negro as are also neuroses, melanoma, pediculosis xanthoma and extragenital chancre while one often sees acne cheloidalis dermatosis papulosa nigra, pustular syphilids and granuloma inguinale (Hazen ADS 31: 310, 1933).

See Loewenthal (JTropM 41 187 1941 4 20, 36, 52, 99, 1942) African Negro diseases; H n (SouthMJ 32 276, 1939) ; Lab and Pool (AmJMSc 196 25, 1938), Negro; Clark (JTropM 61 49 1951) climate and race; Arnold (ADS 53 6, 1946) Hawaiians.

Heredity.—Familial incidence is a feature of some dermatoses as in ectodermal dysplasia keratosis palmaris et plantaris and epithelioma adenoides cysticum. Most persons who develop squamous cancer of the exposed skin have inherited their susceptible type of sun-sensitive skins. Syphilitic infection may be acquired by the fetus from its mother during gestation. An hereditary bent toward sensitization of the urticaria-eczema-asthma type is recognized. See Cockayne (Inherited Abnormalities of the Skin Oxford Univ Press, 1933); Lller (JCutRev 43: 657 1941).

Seasons.—Prickly heat pruritus aestivalis and the superficial staphylococcic infections are usually diseases of the summer months. Ichthyosis and psoriasis are generally more troublesome in winter. Diseases of plant or animal origin, such as ivy poisoning, ragweed dermatitis, harvest mite and spider bites manifest seasonal frequency of occurrence for obvious reasons. Climatology especially as it relates to atopic dermatitis and Texas weather was interestingly discussed by Smith and Harrett (ADS 68: 79 1953) who pointed out that moving to a new location not only affects humidity temperature and circulation of air but also influences nervous tension and chemical contacts. Heat and humidity *combine to increase liability to prickly heat*, bullous impetigo and *hidradenitis* especially when the minimum temperature remains high (Horne: JID 18: 10 105) See Physiology keratin; Dermatitis due to defatting; Anhidrosis.

Occupation.—Numerous irritants are used in both household work and trades, and so frequently do these various substances give rise to dermatitis that occupational dermatoses (q.v.) comprise an important class of dermatoses of medicolegal importance.

Coexisting Organic and Constitutional Diseases.—Sometimes the development of a cutaneous disorder largely depends on the coexistence of an organic or constitutional disease. Tuberculosis, scrofuloderma and the tuberculids are frequently closely associated as might be expected. The *relationship of diabetes mellitus to xanthoma diabeticorum*, and *to moniliasis*, pruritus and staphylococcic parasitism is a matter of common observation. The relation of impaired liver function and macrocytic anemia to chronic eczematoid dermatitis has received the attention especially of Ayres et al. (ADS 62 851 1950). Cutaneous manifestations occur in the majority of systemic diseases. See Wiener (Skin Manifestations of Internal Disorders, Mosby 1947); Montgomery (MinnM 22 451 1939).

Deaths from dermatoses were reported on by LeVan and Sternberg (ADS 59 101 1949) the majority they found, having been caused by pemphigus, exfoliative dermatitis and neoplasms, but a toll was also taken by other kinds of dermatitis, stasis ulcers, herpes zoster syphilis *disseminated lupus erythematosus* erythema multiforme and a miscellany of statistically minor causes.

Focal Infections.—A persistent nest of pathogenic microorganisms may reside in dead or diseased teeth pyorrheic gums, tonsil or tonsil tube, paranasal sinuses, vagina, pelvic organs, prostate bladder or rarely appendix or gall bladder. Occasionally escaping from a focus, parasites may provoke ... or complicate cutaneous disease. A skin which has been chemically irritated may be vulnerable to bacteria of the oral flora which were previously unable to invade the skin. In focal infection in the mouth (q.v.) streptococci are the usual agents. Monilia, too, occur in focal infections particularly of the vagina or nails, and cause trouble when opportunity avails.

A focus of infection is defined as a commonly occurring host parasite relationship wherein pathogenic organisms are located in the host in a circumscribed lesion from which they can be eliminated only by mechanical means, such as extraction, excision or plastic repair (Sutton and Andrews ADS 68 774, 1953).

See Editorial (J 133 111 1947) fact, not theory; Edit (J 134 698, 1947), tonsil stumps; Ayres and Anderson (ADS 34 431 1936) ; Van Stoddiford (SouthMJ 36 225 1943), intestinal worms as foci; Elliott (ProcRoySocM 32 747, 1939) bacteremia and oral sepsis; Epstein and Macaulay (ADS 57 736 1948), bullous eruption not cured until infected teeth were removed; Reisman and H ens (J 114 1 1940) conservative; Curtis (JAmDentA 42 88, 1951) against the whole idea; Chobot (J 150 1420, 1952) significance in allergy; Coleman (J 151 330, 1953) "an accepted principle"; Harding and Knopf (NJerseyMSJ 50 153 1953), generalized bullous dermatosis cured by removing infected teeth; Stevens (BGO 63 348, 1954) foci causing recurrent streptococcic infections of the skin, subcutaneous tissues and lymphatics, cases.

PSYCHIATRIC AND PSYCHIATRIC fact r are significant an l are receiving increa ing recognition Because of personality make-up, some people wa h too much scratch too mu h sweat too mu h mistint rpr t or ov remp h ize al ormalities, or perf rm unwholesome act A de mat logi t hould develop hi amateur psychiat ic, ilit y One mu t possess l nol litres regardi g and wide knowledge of how people think, feel, respond, live a l do things if one woul l interpret skin d seases under tan l them and sometimes cure them.

See Psychosomatic t f lermatology; leo (Derma) (J 1 2 86, 1912) Hod son (JIJF 37 1 3, 1918) Klaber t L (JIJI 59 1, 6, 13 191), H Hsmith nd Norton (JIMI 41 193,) 5 f out pati t dermatoses had psychi tric tiologic factors h il nd Goema (AIDS 66 18 1952) P ychotherapy by lermatologi l Wittkower and Russell (Emotional F ct i Skl Diseases, H ber 19 3 214 pp) motion | at t extra t some skin diseases l some ki liseases dist b the emotion , but this book off rs little proof that the disease tudied wer en sed by the path lc psychosom tic tates, according t ;ew (AIDS 65 36 1952) Allison (AIDS 65 499 1952) motion nd ki diseases as observed by Lr sm Wilson (163

Exciting Causes in diseases of the skin may be internal (constitutional) external (local) or both Often it is difficult or impos ible to locate the exact etiologic factor

TRAUMA.—Injury limited t the epid rm heal without scar l y the mitotic out growth of cell in sheet from arl r epith llum and the ew ki can ot be different ted f om the old. Wh n fil rous ti ue i lost or more i produced beca se of gaping f th wou l edges, a scar is l esult l le. Tra ma l trod es microorgani m l to a positio n whi h th ir activity m b l let rion ffect Trauma produces temporary d latlon of capillaries an l so erythema r suffi ient damage f essel wall to allow tra lation a l *whealing or even vascular rupture with result t petechiae and ecchymoses.*

TEMPERATURE.—Burn and snwel t in l scu sed on p 107 ff See also Anhidrosis

LIGHT ha profoun l ffect n the ski Infrared ra are absorbed l y the super ficial la ers while the hort red ra penetrat ml en heat t ssues t lepth of 0.3 m to a temperature high than th f ce itself Ultra iolet ra s hardly pe etrate the epid rmis. Th l ologi all ct region of the spectrum from 3,130 A.U to 2,900 A.U Ultra let ra are absorbed l y th cell a l cause eros b pecific action on the toplasm Pigme tat n nd th abilit t prod ce pigme t are factors differi g n i l luals. Light sen itivit ma be pathologic (see H droa) The effect of irra lia t on f area pa nted with l of bergamot a e much enhanced (see Contact photosen i t zat on) Se ral photosl n zers sen t r e known th presence of which renders th t ssues a t l more susceptil le among these ar eosi acridine and hematoporphyrin. Th t at n f k n ch lesterol l ltra l let light result in the productio of vita m n D

I NIZING RADIATI N —See Treatment x ray ra l um Burn x ray atomic

CHEMICAL SUBSTAN ES affect g th sk from without are cla ified with difficulty Th range from those wh ch affect every ki su h a undil ted nitric ld, to those wh h affect only a few sk n su h a t rpentine or a th of the host f substances th t prov ke dermat tis venenata (q.v) While conce tration and d ration of contact ha e m h to l w th the result of cont ct ndividual ll rgic idios crasy is an equally mport nt fact r Often the first contact evokes pparent response but l t eo tact w th th lt red and susceptible ski pro ok ole t ea t Thi true of such sub sta ces a *the poison of po son ivy;* but wh th so rema n a problem.

T XI SUBSTANCES of chemical nature m affect the k n f llowing i gestion jection Th manner of et on l l o mea u lerstood, and li d l sen itivit highl ariable See Dermat t med mentosa, d Erythem mptomatic

PARASITES —The ski l ormall host to m k nds of saproph tic orga isms. Som f these wave between innocence an l harmf lness so that c rcumstances fa rable to their growth res lt the le lopme t f mptoms. Moisture w rmth, a d da kness re th pri pal of these and so t is that the stout woma in the summert me complains f rrit t on beneath he pe luk l rea t See Ph si logy k n flora

NERVOUS CAUSES.—It probable th t the nervou syst m l a contributory facto the et logy of a umber of d rmatoses (see psy hologi fact rs and ps chosomati aspect) I some of these su h a h perh dros glossy sk and pruritu direct rel tionsh p can be traced, wh le oth rs, such eurodermat t s, alopecia areata and sclerod rma, the evidence h poth tical The e is tendenc for ph si ia s to attribute dermatoses of known origi t nervou nflue ces ju t the lait ttribute troul les to acid the sy tem See Lew and Corm n (NYSJM 4 1959 1947) and Brunner (ADS 57 374 1948)

METABOLI DERMATOSES includ the kin cha ges n d tary a d endocrine disorders. Di turba ces of met bolism of se eral l sses of hemi al m cause cutaneous manifes tation See chapte on Dermatoses Due t Metabol Disorder

NEOPLASTIC DISEASE.—Studies of the nt neous effect of su light, x ra and tar and its derivatives offe as hopef l a prospect as a y field of inquiry into the nature of neoplasia. In the ski the earliest processes can be seen and followed.

ALTERED REACTIVITY (ALLERGY) —See p. 38.

DIAGNOSIS

Confronted by an individual with a skin disease one has a problem to solve A routine of complete examination is indispensable Accuracy and patience are essential Dermatologic diagnosis is eminently based on objective evidence and in general it is wise to look first and ask questions later Gentleness and tact should be exercised especially in dealing with women. Dispensary patients receive the same consideration as private patients. Particularly in cases of puzzling nature the entirety of the patient must be examined. Diagnostic error is more likely to result from incompleteness and carelessness than from ignorance I recommend to the reader who can—and I refer especially to the medical student—that he drop everything at this point and study an article by Waring (AnnIntM 28 1, 1948)

At first glance one notes the apparent age sex and general condition as regards nutrition, hygiene and malaise One looks at all of the eruption removing and replacing clothes if need be and notes specifically the distribution *of the lesions and evidences of grouping then the primary and secondary* gross lesions. Evidence of pruritus is visible as linear scarification and absence of tops of lesions and in chronic cases the nails are worn and polished The type of exudate is seen to be serous, glairy serosanguineous, or purulent. Crusts may need to be removed (benzine is useful) in order to see the bases of ulcers. Scales may be lifted to determine their adhesiveness, noting the presence or absence of uncovered bleeding points. The lesions are palpated, and the sensations of resistance edema induration infiltration or cystic structure are felt. *Important is examination of the lesion pressed under a watch* crystal diascopy which discloses the color unmasked by the presence of capillary blood Apple butter nodules of tuberculous disease are rendered evident; redness of extravasated blood in purpura does not vanish under pressure while that due to simple hyperemia does. The oral mucosa is examined and the condition of teeth gums and tonsils noted. The general and regional lymphatics should be palpated.

At this stage the observer has sufficient data to form a fair idea of the kind of trouble at hand. He has been asking himself whether the complaint is internal or external in origin and whether it is chemical, parasitic or neoplastic in cause But after examination he should know whether the lesion is hyperemic, inflammatory or hemorrhagic whether it primarily affects the skin or skin appendages, whether it is an irritation, infection symptom or general disease or new growth and he should be able to make a canny surmise as to its duration and symptoms. Cutaneous manifestations of systemic disease must be recognized

He may now add to his data pertinent subjective information as to occupation and habits, the duration and sequence of the eruption and the complaints of itching pain or unsightliness. Further questioning of the patient may be desirable or necessary regarding the functions of the various bodily systems, including the endocrine, and the feelings of the patient and his interrelationships, emotional, sociologic and economic, with other people. These facts are important in formulating treatment, for one must treat the patient, not simply his disease

Scrapings from the lesions digested in 10% potassium hydroxide are examined microscopically if fungus infection is suspected Exudate may be examined for sulfur granules of ray fungus, acid-fast bacilli, streptococci spirochetes. Cultural methods are needed for accurate identification of the mycoses. Biopsy furnishes the histopathologic picture (Rhoden ADS 47 580 1943 Ellis JID 13 26, 1949) Various stains may be applied.

If indicated, a general medical examination must be performed and while few dermatologists excel with the stethoscope they should know how to palpate a spleen The blood picture cell counts, hemoglobin and sedimentation rate while requisite to thoroughness in a hospital are not routinely done in private practice but leukemia or agranulocytic angina is hard to diagnose by guesswork The value of the Kolmer Wassermann and related tests is evident Chemical examination of the blood has its place The blood serum total protein is a significant test of increasing popularity X ray examinations of teeth and sinuses are required in running down focal infections roentgenograms are indicated of tumors attached to bone and of vertebrae long bones and skull in search of metastases. Spinal fluid must be examined in syphilitic patients. The basal metabolic rate may be informative (Leszczynski AnnderD 10 177 1939)

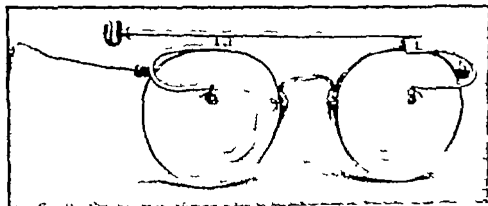


Fig 47 —Magnifying spectacles Accessory lenses, 5 00 spheres with 15-degree prisms, bases in, are mounted in tori strap and pieces connected to hinges on eye wires with L shaped rods allowing unobstructed vision through the distance lenses of the bifocals. Correct collimation and little chromatic aberration, and the glasses may be worn throughout the working day with 2 X magnification immediately available a great aid in both diagnosis and minor surgery (Sutton J 155 1156 1934)

Dermatoscopy by slit lamp or corneal microscope reveals the horny layer and epidermal portions of sweat gland ducts and hair follicles, the pigment and the most superficial blood vessels. Suitable apparatus is expensive and seldom used (Michael ADS 8 603 1923) Surface microscopy using dissection and metallurgic instruments may yield useful information (Goldman and Younker JID 9 11 1947) Photographs may be taken which actually magnify the skin surface (Siebentritt JID 13 281 1949) Capillary microscopy was described and its practical value overestimated by Gilje et al (ADS 68 136 1953)

Diagnosis aims at determining etiology as well as classification. Patch tests and intracutaneous sensitivity tests are further methods of attack. The inquisitiveness and ingenuity of a Sherlock Holmes are required in the elucidation of many problems (Klauder ADS 68 363 1953) Despite the greatest diligence in the attack and the use of the most modern apparatus a physician who is honest with himself is with disconcerting frequency confronted by his own ignorance

Wood s Light has considerable diagnostic utility especially in the treatment of tinea capitis (q v) Fluorescence diagnosis was discussed by Costello and Luttenberger (NYSJM 44 1778 1944) and Ronchese (RhodeIslMJ 28 347 1946)

The val bility and Wood light variou colors wh h m reflect ch ges the amo nt t ovarian hormo es in the blood (Edit: BMJ 1 341 1935) I h ldhood the vulva ot fluorescent but w th puberty appears a brow green backgrou d fluorescence which thereaft r contin es, even fter ca trat on or menopause though during reproductive years a purplish hue of variable intensity is seen which becomes m ch darker during pregnancy fading rapidly after parturition (Morto AmJObGyn 68: 334

1954) The dark purple fluorescence appears in menopausal women within 48 hours after the administration of estrogens and fades after their withdrawal. Precise correlation with estrogenic levels of the menstrual cycle was not found by Benson (BGO 92: 14 1951) who attributed most of the reddish fluorescence to porphyrins resulting from red blood cell decomposition.

Fluorescein given intravenously and followed by Wood's light illumination may reveal interesting findings (Lange and Boyd AIntM 74: 175 1944 Herrmann JID 7: 210 1946 8 421 1947) In general inflammatory lesions imbibe fluorescein and so manifest intense fluorescence while dead tissues do not stain. The method can be used to distinguish vasospasm from embolism or thrombosis and the prognosis of an ulcer associated with varicosity can be estimated, along with the judgment regarding the wisdom of grafting A syphilitic ulcer shows bright fluorescence of the base and poor fluorescence of the margin Wheals and vesicles without blood stasis show rapidly appearing and disappearing hyperfluorescence Inhibition of fluid exchange between the vascular system and vesicular lesions of herpes results in delay in the appearance of fluorescence and persistence of it after it has appeared. Lesions of passive congestion and venous stasis remain dark as in varicosity telangiectasis and rosacea The papules of psoriasis are dark but are surrounded by a bright halo Dark lesions with spotty hyperfluorescence are seen in lichen planus and discoid lupus erythematosus. Clinically as a rule brightly fluorescent lesions will heal while dull lesions respond poorly so that such study has prognostic value

REGIONAL DISTRIBUTION OF COMMON DERMATOSES

Anal Region.—Pruritus, condyloma hemorrhoids, tinea, intertrigo contact dermatitis (soap and medicines) folliculitis o yriasis, phthiriasis, lichen simplex.

Bearded Region.—Impetigo, dermatitis venenata, sycosis tinea barbae, alopecia areata, sinus tract of dental origin keratoses, carcinoma.

Breasts.—Dermatitis venenata, infectious eczematoid dermatitis, carcinoma, Paget's disease, scabies intertrigo.

Chest and Shoulders.—Seborrhea, acne syphilids, tinea versicolor seborrheic keratoses, scabies, psoriasis, pediculosis, drug eruptions, the acute exanthems.

Crural and Axillary Regions.—Tinea, seborrheic dermatitis, intertrigo, dermatitis venenata, streptococcic dermatitis, scabies, furunculosis hidradenitis, infectious eczematoid dermatitis.

Ears.—Seborrheic, bacterial, or chronic lichenoid dermatitis, keratosis, carcinoma frostbite painful nodule.

Eyelids.—Dermatitis venenata, xanthoma palpebrarum, molluscum contagiosum, keratoses, stye, chalazion atopic dermatitis, seborrheic dermatitis. (Hazen ADS 49 253, 1944; Ormsby: AmJOphth 26 850 1943.)

Face.—Freckles, chloasma, vitiligo, seborrheic dermatitis, dermatitis venenata, impetigo erysipelas, acne, rosacea, milium, rhinophyma, syphilids, lupus erythematosus, erythema multiforme lupus vulgaris nevus, angioma, seborrheic keratosis, carcinoma, herpes simplex, molluscum contagiosum. (Thorek The Face in Health and Disease Davis, 1946.)

Forearms and Legs.—Infectious eczematoid dermatitis, dermatitis venenata, ecthyma, urticaria, lichen planus, psoriasis, erythema multiforme, erythema nodosum, purpura, ichthyosis, keratosis pilaris, syphilids, atopic dermatitis (flexures) lichen simplex, stasis dermatitis, bites purpura.

Genital Region.—Pruritus, scabies, pediculosis, seborrheic dermatitis, herpes simplex, chancre, chancroid, lymphogranuloma venereum, syphilids, lichen planus, carcinoma, dermatitis venenata kraurosis, lichen sclerosus, lichen chronicus simplex, tinea.

Hands and Feet.—Vitiligo, tinea, dermatophytid, dermatitis venenata, streptococcic dermatitis, scabies, hyperidrosis pompholyx, palmar and plantar keratoses, infectious eczematoid dermatitis, erythema multiforme, syphilis, dermatitis repens, verruca, carcinoma (hands) x ray dermatitis. (Madden, Nomland, Caro, Montgomery Kulchar: J 124 743 ff 1944, feet; Lane JMichSMS 39: 649 1940, hands; Sutton and Ayres: ADS 68: 226 1953, hands.) Examination of the hands yields valuable clinical information (Silverman: J 155: 902, 1954); when the palmar creases have lost their reddish color the hemoglobin is likely to measure less than 7 Gm./100 cc. (Wintrobe Clinical Hematology Lea & Febiger 1951)

Lips.—Herpes simplex, leukoplakia carcinoma, chancre, mucous patches, cheilitis exfoliativa, cheilitis glandularis apostematosa, Fordyce's disease urticaria, retention cysts, contact stomatitis, lupus erythematosus, fissure.

Neck.—Lichen simplex sebo rheic dermatiti lermatiti venenata (wool fur cos metic) cutaneou tags.

Scalp.—Seborrh i dermatiti dermatiti enenata psoria i tinea (children gen rally) lupu rythematosus, pediculosi apiti i fection ec ematoi l l rmatiti pre mature al pecia, al pecia areata s phili s zruta seborrheic v t n s furun les ne necrotica.

Tongue.—Leukoplakia, carcin ma, transit v benign pl p es bornlag t gu lingual ton illitis yphili avitaminosis, m roesti ab mia, korda i mpani s ndrome

Trunk.—Dermatiti venenata infection eczematoid l rmatitis, purpura seborrh i d rmatiti pit ria is rosea, urticaria h rpes zost r syphilis, psoria is, seborrh i keratosis, scabies pediculosi xanthemata.

See Sabouraud (Regional Topographical Dermatology M rshall Translation, Rebman, 1986)

TREATMENT

Treatment to be successful must accomplish aims which themselves depend on a rational plan and the plan depends on correct interpretation of the disease and the personality Empirical dermatologic therapy is obsolescent. Only the minority of patients nowadays receive treatment which has been prescribed solely because such treatment has helped other patients with similar troubles.

The cleverest plan of treatment is a failure if the patient is not adequately instructed in carrying it out or if the patient cannot be so controlled by his physician that he does what he is asked to do It is unfair and incorrect to ask of a patient what is, for him impossible In possibly half the cases the dermatologist sees cure requires keeping something off the patient rather than putting something onto him or into him. In ordering medication one should not omit the stop order for persistent, unnecessary use of medicines is objectionable and often harmful

A patient is likely to cooperate if he is told why he is asked to do or take something in a certain way Intelligence in the patient may be hoped for but cannot be expected While this fact adds to the physician s difficulties, it also adds to his responsibilities. There is no doubt that rapport, confidence and encouragement play an important part in delivering that for which the physician s services are engaged This aspect of what goes on between physician and patient would by some be called psychotherapy In diminishing the suffering of the sick the laying on of hands has a reputable and ancient history The physician who lacks ability to inspire confidence assuage fears and shoulder burdens for his patient works under a great handicap. In fact lacking the ability to learn to do these things, he should be in another business.

It is not correct to presuppose that the patient is too obtuse to comprehend the nature of his illness and the plan for his betterment. I believe in telling him in language I think he can understand just what is going on, in sofar as I know I willingly confess ignorance when that is the case and thereby justify such diligence, investigation and consultations as are indicated. I label prescriptions so that the contents are identified. This policy differs from that popular several years ago when a doctor might have been taken on faith alone for seldom nowadays is he so taken. It is a conceited man who supposes that the laity are ignorant the truth is that only some of them are A doctor must impose his will on his patient and this can be done best with graciousness, diplomacy and reason.

The handling of patients is a challenging art, in which a physician may throughout his life hope to improve himself. Medicine is a ministerial profession, wherein the desire to be helpful is the basic necessity A good doctor lives by this. He is intuitively sensitive to emotional as well as to bodily needs. He must be an honest man who thinks clearly who possesses stability who can give to others sympathy courage and confidence. He is able to make his good influence felt. He knows that illness and fear go hand in hand, and his gentleness, tact truthfulness, strength and warmth relieve fear which is harder to endure than pain and give comfort. Where cure cannot be obtained palliation may be achieved with resourcefulness A patient can be helped to bear that part of his suffering which cannot be escaped. When death comes, still the doctor serves well if he is kind of heart and understanding and sees to it that all is done that can be done for the patient and the family (Alvarez J 150 86 1952)

Neck.—Lichen simplex, seborrheic dermatitis, dermatitis venenata (wool, fur, cosmetic), cutaneous tags.

Scalp.—Seborrheic dermatitis, dermatitis venenata, psoriasis, tinea (children generally), lupus erythematosus, pediculosis capitis, infectious eczematoid dermatitis, premature alopecia, alopecia areata, syphilis, wen (sebaceous cysts), nevi, furuncles, acne necrotica.

Tongue.—Leukoplakia, epithelioma, transitory benign plaques, burning tongue, lingual tonsillitis, syphilis, avitaminosis, macrocytic anemia, chorda tympani syndrome.

Trunk.—Dermatitis venenata, infectious eczematoid dermatitis, purpura, seborrheic dermatitis, pityriasis rosea, urticaria, herpes zoster, syphilis, psoriasis, seborrheic keratosis, scabies, pediculosis, exanthemata.

See H. Gougerot (Regional Topographical Dermatology, Marshall Translation, Robinson, 1936).

CHEMICAL AGENTS

Adrenocorticotropic Hormone (ACTH) and Cortisone.—ACTH was developed by Armour Laboratories as an outgrowth of the researches of many investigators on Addison's disease, adrenalectomized animals and the relationship of the pituitary gland to the adrenal. After a pituitary extract was found which prevented the atrophy of the adrenal glands which results from removal of the pituitary gland in animals there was achieved a quantitative bioassay method which enabled more precise chemical fractionation of pituitary extracts, and accurate study of the effect of ACTH became possible. Eventually the hormone was produced in adequate amount and satisfactory purity for use in human beings, so that Thorn et al. (NEngJM 41: 829 1940) were able to report that the adrenal gland, though seemingly in a state of exhaustion, was capable of responding to stimulation.

Injection of ACTH is known to cause a marked drop in the number of circulating eosinophile leukocytes, an increase of the uric acid-creatinine ratio in the urine, an increase in the urinary excretion of 17-ketosteroids and 11-oxysteroids, the retention of sodium chloride and the increased excretion of potassium and nitrogen in the urine of normal human beings. The effect of ACTH on the collagen group of diseases, which dermatologically includes lupus erythematosus, acrosclerosis and dermatomyositis, became known. The contraindications including peptic ulcer, diabetes mellitus and liability to development of Cushing's syndrome were recognized. Notable improvement in 4 cases of systemic lupus erythematosus were reported on by Elkinton et al. (J 141: 1272, 1949) and the literature since has been replete with studies of dermatologic import regarding ACTH.

Cortisone has an interesting history beginning with the isolation of numerous crystalline compounds from the adrenal cortex by Kendall and co-workers. Of these compounds only 4 showed significant physiologic activity and were designated as compounds A, B, E, and F. *All were derivatives of delta4 pregnene and differed chemically from one another* only by the number and position of hydroxyl and ketone groups attached to positions C-11 and C-17. Hench observed that rheumatoid arthritis is ameliorated by jaundice and by pregnancy and it was on this basis that he was anxious to use compound E (cortisone) experimentally for this condition. A small supply became available from Merck and Co., who by 1948 had been able to achieve production sufficient for limited purposes. The amazing value of the chemical was at once apparent, and subsequent improvements of production methods have made it available in large quantities at a relatively low price.

Differing from ACTH, administration of cortisone is supplemental adrenal therapy rather than adrenal stimulation therapy. While the indications and contraindications of the two substances, as well as their effects on disease processes, are to a considerable degree similar, yet the differences are significant. Cortisone is, in general, more effectual and less likely to result in harm, for ACTH stimulates more than the adrenal while it stimulates that gland to produce more than cortisone, and the ill effects, when they occur, are of wider variety and more lasting duration.

Both drugs have the capacity to depress mesodermal allergic reactivity (Green: BMJ 1: 1165, 1950). While they have been recommended for use in contact dermatitis, I have not witnessed great virtue in this regard. Their value in pemphigus, systemic lupus erythematosus, atopic dermatitis, lichen chronicus simplex and autoeczematization, exfoliative dermatitis, psoriasis, drug eruptions, scleroderma, erythema multiforme, purpura, syphilitic iritis, interstitial keratitis, Addison's disease and the lymphoblastomas is discussed under those headings.

I have not observed that relapses after withdrawal of cortisone, when its administration has been effectively palliative, are worse than they would have been had the chemical been withheld. Cortisone and ACTH may light up and exacerbate quiescent peptic ulcer, the presence of which denies their use in a given case (Gray et al. J 147: 1529, 1951). They may activate tuberculous infection (Edit. J 145: 907; 147: 260, 1951) and caution is requisite. The patient with systemic lupus erythematosus given cortisone by Harris-Jones and Pein (Lancet 2: 115, 1953) developed miliary tuberculosis. It is dubious that they interfere with wound healing, although this has been reported (Billingham et al. BMJ 1: 1157, 1951). The tendency to promote infections by a mechanism as yet unexplained was reviewed by Thomas (AnnNYAcadSci 56: 799, 1953); perhaps there is some suppression of antibody formation. Judging by the effects on experimental inoculations of mice with streptococci, Lötzsch and Eichoben (DWehn 1?3: 653, 1953) could find no evidence that cortisone favors the spread of infection. The minimal effective dose of antibiotics is slightly increased when cortisone is given (Jawetz and Merrill: Sci 118: 549, 1953).

Other contraindications are hypertension, impaired renal function, personality disorders, Cushing's syndrome, impaired cardiac reserve, polycythemia, osteoporosis and diabetes mellitus (Callaway et al. SouthMJ 45: 63, 1952). The prolonged administration of cortisone is thought to depress the activity of the adrenal gland, which will on this account eventually undergo atrophy (Kendall: AnnIntM 33: 787, 1950) though this is reversible. This is the argument long attached to the use of thyroid and not as yet dead, though moribund. No harm comes, I believe, of proper dosage for cortisone, like thyroid, is replacement therapy supplementing the body's own chemical substances; the right dose is good, the wrong dose is not, for underdosage accomplishes nothing and overdosage does harm. There is no reason why the patient may not take the right dose throughout a lifetime. A patient with Addison's disease must. Osteoporosis resulting in multiple pathologic fractures of the spine was caused in 4 men who received prolonged cortisone and ACTH treatment, observed by Curtis et al. (J 156: 467, 1954).

The drugs are antagonistic to the *anticoagulant activity of ethyl biscoumacetate* and this may account for the thrombo-embolic phenomena that sometimes complicate their administration (Cosgriff: AmJMed 9 5 1950; Chatterjea and Salom: BMJ 1 790 1951). This antagonism may account too, for their palliative effect in urticaria pigmentosa.

When cortisone therapy was abruptly discontinued in asthmatic patients there developed within 1 hour headache and aches in the muscles and joints reported Henn man et al. (J 1 8: 351 19 3). The symptoms while sometimes alarming lasted for only a few days, subsided spontaneously and were not associated with significant changes in vital signs or laboratory tests. A death in status asthmaticus was described in a boy with Besnier's prurigo following the cessation of cortisone and ACTH medication (BMJ 2: 1307 1951).

The influence on skin tests and passive transfer phenomena have been studied and Zeller et al. (AnnAllergy 8: 163, 1950) as well as Feinberg et al. (JAllergy 22: 195 1951) found no effect on immediate wheal reactions or skin reactions to antigens or to histamine while ragweed dermatitis was unresponsive to the administration of ACTH or cortisone. Yet cortisone does appear to depress the reactivity of the connective tissues (Plotz et al.: AIM 61: 919 1950) and in a patient hypersensitive to antipyrine the rash would not develop while the patient took cortisone (Goldman and Hockwald: AIM 61 911 1951).

Compound F (17 hydroxycorticosterone-21-acetate) has physiologic effects similar to those of cortisone acetate and was said by Goldman et al. (JID 18: 89 1952) to inhibit the development of a diagnostic patch test when cortisone did not. Local intracutaneous injection of compound F marvelously palliative in some cases of arthritis when put into the joint have proved helpful in lichenoid dermatitis and a variety of dermatoses, inhibiting cutaneous reactivity (Goldman and Preston: ADS 67: 163, 1953).

Topically cortisone has one notably valuable application in the treatment of syphilitic iritis (q.v.) but despite the report of Spies and Stone (SouthMJ 43: 871 1950) it may safely be said that cortisone ointment has little or no value in any other dermatologic condition (see Goldman et al.: ADS 65: 11 195-). Hydrocortisone acetate ointment has attained great popularity (Sulzberger and Witten: JID 19 101 195-; Sulzberger et al.: J 151: 468 1953; Sulzberger: ADS 68: 451 1953; Baer: ADS 68: 4- 1953; Sidi et al. PresseMéd 61 997 1953). Its effect may be gratifying in atopic dermatitis, lichen chronicus simplex, especially when that of anogenital location, pruritus ani, and chronic eczematous dermatitis of the eyelids, ears or hands. During 1953 we saw it used without advantage in many a case responsive to less recent advances in modern therapeutics. Hydrocortisone, the free alcohol, was said by Sulzberger et al. (J 15- 1450 1953) to possess all the virtues of the acetate when used topically. The incorporation of an antibiotic in hydrocortisone ointment preparations has become popular. It is effective clinically for the dermatoses for which hydrocortisone is indicated and which are complicated with pathogenic bacteria. One of the good combinations is Terramycin with hydrocortisone as attested by Strauss and Frank (AD 71 736, 1955). Quantities of hydrocortisone have been applied unnecessarily but clinicians as well as patients are interested in results, strict science being, from the practical standpoint, somewhat tedious.

See Sulzberger et al. (JID 16 373, 1951; ADS 64 573, 1951); Lever (NEngJM 46 189, 1951); Stollerman et al. (ProcSocExperBiol 76 41, 1951): cortisone does not interfere with passive transfer when given either to the donor or the recipient; Baldridge and Kligman (JID 1 287 1951): cortisone without influence on elicitation of experimental contact dermatitis; Nilzen (JID 18 7, 1952): cortisone delayed reactions in experimental eczema; Kierland et al. (J 148 23 1952); Fisher and Walton (CMAJ 74 5- 1952): benefit in topic dermatitis, drug eruptions, pemphigus; Fischel et al. (ProcSocExperBiol 81 344, 1951): cortisone interfered with antibody formation induced by booster doses of antigen given to rabbits; Sulzberger and Baer (YBD 1952, p. 7): extensive essay on ACTH, cortisone and compound F; O'Leary and Erickson (J 18 1498, 1952): temporary benefits, not cures; Med. Research Council (BMJ 2 1400 1953): hematologic applications; Robinson and Robinson (J 155 1212, 1954): hydrocortisone acetate topically less than 1% ineffective; addition of antibiotics advantageous; Heilesen et al. (ADS 70 300 1954): use in lichenified eczema, especially anal; Sulzberger and Witten (J 155 934 1954): long term study showing no addiction or tissue resistance; dose generally can be reduced; Fuhrman and Downs (JIowaMS 55 322, 1954): hydrocortisone-neomycin ointment harmless; Med. Research Council Rpt. (BMJ 2 1307 1954): ACTH and cortisone in dermatology; McCorriston (CanadMAJ 70 59, 1954): topical in atopic infants, no contraindications; Church (BMJ 1 517 1955): topical for eczema, palliative but sometimes spreading infection; Witten et al. (JID 24 1 1955): topical fluorohydrocortisone acetate effectual, seldom irritating; Robinson (J 157 1300 1955): fludrocortisone acetate ointment 0.1% effective; Lubow (AD 72 164, 1955): 9-alpha fluorohydrocortisone ointment rarely irritant, usefulness analogous to that of hydrocortisone topically; Wright et al. (AD 72 69 1955): 9-alpha F no better than hydrocortisone.

Aerosporin.—See Antibiotics, polymyxin.

Androgenic and Estrogenic Chemicals.—Since testosterone has value in managing menopausal disorders it has some applicability to dermatoses like keratoderma climactericum (Wells et al. JID 15: 391 1950) and to postclimacteric dermatoses in the aging male (Hollander and Vogel: ADS 45 356 1942). The ability of testosterone to provoke acneiform eruptions is well known, and the acne it causes is hy... Its influence on sebaceous glands is pronounced. A dose of 3 mg daily will probably not induce virilism.

The naturally occurring estrogenic hormone was identified and obtained in crystalline form by Doisy et al. (AmJPhys 90: 329 1929; JBiolChem 87 357 1930). Like any other hormone, estrogen is indicated when there are evidences of its insufficiency. A simple clinical criterion involves only a clear history in the acneic girl of menses which last for 6 days or more, with tenderness of breasts at the start and perhaps cramps. The occipital headache, nuchal tension and hot flashes classically symptomatic of deficiency of menopause are often found in young women, who may be greatly relieved by the oral administration of a suitable dose, such as Premarin, 0.3 mg., sometimes 0.625 mg daily

Many cases of acne (q v) both in males and in females respond well to estrogen a fact stressed by Goeckerman and Wilhelm (ADS 66: 40* 105.) Psoriasiform eruptions, scattered lichen old dermatitis and seborrheic dermatitis of the palms may respond well according to Drant (PaMJ 5.: 966 1949) Senile atrophy may respond especially if it involves the genitalia of elderly women. Lamb et al. (ADS 57: 785 1935) reported on the use of these substances in lupus erythematosus and polymorphous photosensitive eruptions. Lichen simple in a flare l often made worse.

Topically estrogenic substances ar absorbed through the skin from an ointment vehicle and produce systemic effects while the ski itself shows epithelial proliferation in postmenopausal females with thin dry i teguments (Eller and Eller ADS 59: 449 1949) Overdosage and severe menorrhagia d veloped in a woman treated with an estrogenic ointment and reported by Goldberg and Harris (J 150: 00, 105) Such ill effects are reversible on withdrawing the hormone (Shapiro: JClinEndocrl 1 : 51 1052) While no ill effects resulted from adding estrogenic ubstances to emollient creams for use on dry ski s, no extra benefits accrued s observed by Behrman (J 155: 119 1954)

Marisone is a steroid complex ol tai ed as a by product in separating estrone from the urine of pregnant mares. According to Duemling and Millman (ADS 65: 327 195.) it has beneficial effects in various skin diseases including pemphigus contact dermatitis and keratoderma climactericum. It is useful in atopic dermatitis a d chronic urticaria and is well tolerated (Spielman and Blau: ADS 66: 488 1952)

Anthralin.—See Reducing substances.

Antibiotics.—These chemical substances, produced by some living organisms and antagonistic to certain ther living organism posses a wide range of values in the treatment of many kind of parasitic dermatoses. New ones are continually being discovered, and their evaluation continues to evoke a massive literature, while the capabilities of those longer known are becoming better and better tandardized (Flory: J 135: 104 , 1947; Baron: Handbook of Antibiotics, New York Penick & Co., 1950, pharmacology of 141 anti biotic drugs) An excellent reference book is that of Welch and Lewis (Antibiotic Therapy Medical Encyclopedia Inc., 1953) which includes biographic sketches of the discoverers, as well as the chemistry toxicity and utility of the substances themselves. See also Wel h (The Manual of Antib otics Medical Encyclopedia, New York, 1954, 87 pp.) Thus it is known that penicillin cures syphilis, and so is the standard agency for treatment of this disease. Methods of choosing antibiotics have attai ed a solid basis. It is now a commonplace laboratory procedure to isolate presumably causative organisms, to test their sensi tivities to various antibiotic medicines and to use that chemical which best antagonizes the particular species and types of infections present (Spaulding and Anderson: J 147: 1336, 1951 practical technic) The a tiparasitic spectrum of each antibiotic has been carefully tested and is becoming common knowledge with respect to particular organisms. Thus one expects to find som strains of staphylococci not responsive to penicillin but responsi e perhaps, to Aureomycin o to find in an ear canal *Pseud monas aeruginosa* which may pe haps be eradicated by neomycin but would not be responsive to Aureomycin, which fact the physician would nowadays know in advance

Correct use of antibiotics requires competent laboratory guidance and a good knowledge of what the drugs are able to do both fo the welfare and to the detriment of the patient. All of them have potentialities for harm, a feature which they share with every other substance with which a physician may wish to treat a patient.

Some antibiotics work together to the advantage of a patient, and others antagonize one anothe (Edit. BMJ 2: 1160, 1950) It seems, fo example, that chloramphenicol negates the effect veness of penicillin. Combination of chemotherapeutic drugs may o may not be wise, depending on factors not as yet fully understood (Edit.: J 147: 512, 1951) Thus while para-aminosalicylic acid and dihydrostreptomycin may together constitute a strong attack on tuberculosis, Aureomycin-penicillin combinations may or may not affect staphylococcic infections favorably depending in part on the concentrations employed. Antibiotic preparations for topical use commo ly contain more than one agent. Terramycin ointment was put up with polymyxin B standardly 1953, for xample, and many othe combinations could be listed designed to improve the antiparasitic spectrum of the product.

Topical Application of many antibiotics is of great practical value in dermatology although penicill may ot be so used because it irritates or sensitizes many individuals. Studies of th injurious effects of arious concentration of various antibiotes were made by Cruickshank and Lowbury (BMJ 2 1070 1952) and are of fundamental importance in adjusti g the concentrations to be employed. These n estigat rs and also Hu t al. (JID 20 357 1953) observed that human tissue cult es suffered toxic effect if the following concentrations were exceeded

Aureomycin	0.2 mg./cc.
Terramycin	0.2 mg./cc.
Chloromycetin	0.01 mg./cc.
Polymyxin B	0.2 mg./cc
Penicillin G	0.6 mg./cc.
Neomycin	1.0 mg./cc.
Gramicidin	0.001 mg./cc.
Bacitracin	0.01 mg./cc.

The inhibitory concentrations and the effects on the skins of patients are not completely parallel, for neomycin and bacitracin are not u ually toxic when applied topically while penicill n often i

THE EFFECT ON THE NORMAL FLORA of antibiotic medications I of int rest (Edit.: J 149: 6., 1181 19.) New infection with organism n t sen itive to the medicine being given may dev l p so to complicate th original disease The suppressi n of one organism may allow anoth r to luxu iat Monilia is (q.v., etiology of) is thought commonly to supers n when Aureomyc penicillin or chl ramphenicol has been given for a con iderable period of time Th re I a question a to wh ther the virulen e of the fungus i actually enhan ed. Sore mouth black hairy tongue (q.v) thru h and diarrhea with monilia abundant in th stool have been observed d ri g antibioti therapy (McGo ern et al.: NEngJM 45: 39 1953) possibly a a res lt of elimination of competition between the sen itive orga m an I the insensitive on Chro ic pulmonary monilia i and even fatal ill es have been known to volve a complicati ns (Brown et al.: J 152: 206 1953) Prot us an I P udomonas i sen itiv to many antibiotics, ha e been known to multiply so as to become path ge ic. As a rul discontin nce of the antibiotic has been followed by restoration after a time of the norm l balance of the fl ra.

ACHROMYCIN —By removing the chlorine at ms from Aureomycin, a new antibiotic tetracycline more soluble and more stable ha been d veloped (Put am et al.: Antibiot& Chemother 3 1153 1953) The spectrum is almost identical with chlort tracycline and oxytetracycline (Fi land et al.: J 1 4: 561 1954) Apparentl prod cing less gastroent ric irritation than the others Achromycin quickly ha become a favorite antibiotic of great excellence in m experience Th ointment i al I le a d nonirr tating See Council Rpt. (J 15 13 1954) t tracycl n A bromy in (Lede le) Tetra n (Pfiz); Robinson et al. (SouthMJ 45: 516 19..) no positiv pat h test t tetra li among 023 patient treated with the 3% oi tment.

AEROSPORIN.—See P lymyxin.

ANTIFUNGAL ANTIBIOTICS.—A strai of B. subtilis wa nh bitory to T. schoenleini gypseum reported Lewi et al. (ADS 54: 300 1946) Clavacin in vitro effectively inhibited M albicans T gypseum T purpureum and especially M and n according to Loewenthal and Tolmach (JID 8 33 194 0 41 194) Fungicidin the name given an alcohol extractable sub tance obtained from the growth of a soil cti om cete by Hazen and Brown (Sci 11 : 423 1950) and it was ffective i itro aga nst C lbica Cryptococcus coformans, H capsulatum B dermatitidis Coccidioides imm i s, T rubrum and T gypseum Mice injected with a lethal mixture of Aureomycin and Candida albica were saved by a preliminary injection of fungicidin (Brown et al.: Sci 11 609 1953) One fraction of neomycin as it was prepared by Swart et al. (P&ExpBiol 3 376, 1950) is f ngicidal (see Edit. J 144: 630 1950) Th olutin, an antibiotic isolated from several strains of Actinomyces was tried b Fra k (JID 19 209 195.) in the treatment of h man tinea capitis w th encouraging although not spectacular result Mycostatin, ol ta ned from Streptomyces ruber rapidl inact ted u less stored in a vacuum, a d high in t se t pro ed act e n vitro against C m ts H capsulat m, B dermatitid S schenck and M audou i, reported Burke et al. (JID .3 163, 1954) N statin, a more h peful preparation, being nont xic is discu sed under Mon lia is treatment (q)

The subject, f great interest but with as yet l ttle practical applicat on, was reviewed by Wooldridge (SouthMJ 45: 351 195.) who noted that actid on u fortunately toxic ah b ts Cryptococcus neoformans, and prodigiosl appears to ffect coccidioidal infect on significa tl See Lechevali r (I resseM 61 1327 1953) 4 nt f gal nt b ot cs from actinomyces candicine of dubiou cl nical value; Kl gman and Lewis (P&ExpB ol 8. 200 1953) c a licine strongly a tif ngal n vitro aga nst major h man pathogens, excepting Coccidioides imm tis and ringworm parasites.

AUREOMYCIN (CHLORTETRACYCLINE) derived from stra of Strept rcofac a ellow crystalline hydrochloride salt sol ble in wat d unstal le in alkaline solution (Brosch rd et al. Sci 109 119 1949) It is ct e aga t um rous gram posit e and gram negat e bact ria ncluding st eptococci staph lococci Kl bsell pneumoniae Hemophilus ducreyi Brucella suis and Br abortus. Pseud monas ruginosa and strains of Proteu were not inhibited by a concentration of 70 µg/ml. (Bry et al. J 138 117, 1948) It i rap dly excreted in the urine eachi g highest concentration within from 4 to 16 hours so that t hould be given at nt rvals of from 8 to 8 hours (Finland t al.: J 138 946, 1948 It is ti e against many rickett oses, especially Rocky Mount in spotted feve (Ha rel et l. SouthMJ 4. 4, 1949) and is useful ma y infection in which penicillin is mpotent (Finland et al AnnIntM 31 39 1949) It probably s curat e in the treatme t of syph lis (q v) Its utility in h rpes ost d dermat ti herpetiformis is in my opi ion, highly d bious. The large doses gi in th earl days f it introduction into medical therapy were often ill tolerated, with diarrhea om ti g d rritation of the anal d oral mucosae, a w ll as those of the gut, but wh n gi en with m lk d in moderate dosage t is a highly effective remedy f those infect on for which it is indicated. It is the best agent in lymphogran loma venereum, accord g to Robinson (AmJSyph 34 273, 1950)

Topically 3% Aureomycin in petrolatum is indeed welcome dermatologic medicament. It irritates seldom, if ever, and serves well in impetigo i fectious eczematoid dermatitis and secondarily infected contact d rmat t s. It is a good prescription for

herpes simplex. On a leg ulcer overlaid by a boot such as Medicopaste, it performs well as a bland, bacteriocidal unguent. Patch tests by Siegel and Schantz and by Hollander and Hardy (abs ABD 1950 p. 68) were negative. See also Robinson and Robinson (South MJ 44: 1116 1951)

BACITRACIN is used only topically A product of a bacterium of the *Bacillus subtilis* group it is a neutral, water-soluble relatively heat-stable substance with activity parallel to that of penicillin It is, however far less likely to irritate or sensitize than penicillin is when used topically It is valuable in superficial infection with bacteria (Miller et al. JID 10 179 1948, ADS 60: 106 1949; Meleney and Johnson: J 133: 675, 1947; Derzavis et al.: J 141: 191 1949; Flanerty: NEngJM 15: 14 1951) In Polysporin it is mixed with aerosporin and polymyxin, and the antibiotic spectra of the ingredients complement one another

CARBOMYCIN (MAGNAMYCIN) obtained from *Streptomyces halstedii* is active against gram positive bacteria, but some strains of *Micrococcus aureus* develop resistance readily and there is a high correlation with the effect of erythromycin (Hewitt and Wood: NEngJM 49 761 1953) Good results have been obtained in pneumococcic and streptococcic diseases with doses of 500 mg by mouth at 6 hour intervals. It appeared effective in granuloma inguinale (Whitaker et al.: AmJSyph 37: 400 1953) See Edit. (BMJ 1 14 1, 1953)

CHLOROMYCETIN (CHLORAMPHENICOL) was originally obtained from a new strain, *Streptomyces venezuelae* by Burkholder (Ehrlich et al.: Sci 106 417 1947) It is a bitter crystalline compound of known chemical composition showing marked chemotherapeutic effectiveness against several rickettsial and virus diseases as well as a wide range of gram negative and gram positive bacterial infections (Edit.: J 138 432, 1948) Unfortunately its internal administration has resulted in occasional but tragic ill effects on hematopoiesis. It was trusted for several years before this fact became generally known from a series of articles in J.A.M.A as well as elsewhere and several victims of fatal aplastic anemia were children of physicians (J 149: 231 01, 1203, 1301 193; see also Dermatitis medicamentosa) Yet its effectiveness in typhoid fever (Woodward and Smadel: AnnIntM 29: 731 1948) typhus (Woodward: AnnIntM 31: 53, 1949) and other rickettsial diseases as well as brucellosis (Smadel: J 142: 315 1950) keeps it from being discarded from internal medicine while topically it is harmless in appropriate concentration possessing great utility against *B proteus* and *Ps. aeruginosa*. Newman and Feldman (ADS 64 1951) observed neither irritation nor sensitivity in 51 cases of pyogenic dermatitis treated with a 1% concentration in a vanishing cream. Trice and Shafer (J 140: 1460, 1952) and Pauletta (GlobitalD 93 07 1952) likewise reported favorable experience. I have used Chloromycetin topically incorporating 7 milligrams per gram in Vioform Cream, on thousands of patients with superficial infections, without ill effect attributable to the antibiotic and with great satisfaction. See Marleonda and Montilli (Dermatologica 4: 13, 1953)

CLAVICIN —See Antifungal antibiotics.

ERYTHROMYCIN (ILOTYCIN) is produced by a strain of *Streptomyces erythreus* and possesses high effectiveness against pneumococci and group A hemolytic streptococci (Haight and Finland: NEngJM 47 227 1952) Other streptococci, staphylococci and Neisseria organisms were somewhat less sensitive as were also the strains of Hemophilus and of diphtheria bacilli. Coliform bacilli, Proteus, and Pseudomonas organisms were all quite resistant. On a weight basis, erythromycin was essentially similar in its activity to penicillin; it was more active than the broad spectrum antibiotics against the gram positive organisms, less active against the gram-negative coliform bacilli, and about equally active against strains of Hemophilus The antibiotic is often active against penicillin resistant staphylococci, though not in all cases, and does not seem to be as effective as penicillin in gonorrhea. Several cases of staphylococcic septicemia were cured with this drug by Herrell et al. (J 152 1601, 1953), who reported no serious toxic reaction I have seen erythrodermas it caused. Topically applied in 1% concentration it proved effective in pyodermas treated by Robinson and Zeligman (JID 20 405, 1953) and by Freeman and Scott (JPediat 4 669 1953) without inducing sensitivity It was combined with neomycin by Livingood et al. (J 153 1266 1953) whose report was not extremely enthusiastic. Strains of *M pyogenes* resistant to erythromycin are being seen frequently (Martin et al. PSMMC 29: 379 1954) See Kirby et al. (AIntM 92: 464, 1953); Robinson et al. (ADS 0 825 1954)

GRAMICIDIN —See Tyrothricin.

ILOTYCIN —See Erythromycin.

MAGNAMYCIN.—See Carbomycin.

NEOMYCIN isolated by Waksman and Lechevalier (Sc 109 305 1949) from a soil organism, *Streptomyces fradiae* is a water-soluble, thermostable basic compound active against various gram positive gram-negative and acid fast organisms and Actinomyces. Kile et al. (ADS 65: 511 1950) were enthusiastic about its topical application in a concentration of 5 mg per gram of water miscible base in the treatment of pyogenic dermatoses. While especially active against hemolytic staphylococci, it possesses some potency against *Pseudomonas* and hemolytic streptococci (Forbes: SouthMJ 45 235 1952; ADS 65: 631 1952) Livingood et al. (J 148 334 1952) judged it superior with respect to infections with *Pseudomonas*, *Proteus* and hemolytic *Staph aureus*, especially in ear canal infections, although for *Pseudomonas* infections, polymyxin B may be better (Id.: ADS

(Gi 4a, 10, 4) No sen tization or primary irritation wa observed in thei cases but several in tances of localized monili i d el ped in th m, di appearing after the ces a ti n of the drug Neomycin combined with hydrocortison ointment has earned great popularit

PENICILLIN discovery of which i credited to Fleming (BJExpP 10 226 1929) and early tried in human disease by Abraham et al. (Lancet 2: 177 1941) ha changed the practice of d rmatology The penicilli s all have the empiric formula $C_9H_{11}O_4SN$ R, R being variabl (Sc 102: 627 1945) All are strong m noba ic a id rea ily deteriorated by heat a id an l oxidation. Parent ral admi i tration res lt in 60% urinary excretion, oral only 14% so that 3 to 5 times a much m st be given by mouth a by injection to a compli h the aim (Fr i et al.: Sc 102 606 1945) Serum concentration can be increased significantl b re triction of wat r i tak and b admi tr tion f 2.5 Gm. benz i acid a d 0.5 Gm. sod um hlori l ea h 4 hours while peni illin i bei g gi en (Bronfenbrenn r and Favour: Sc 101: 673, 194) and in other wa s such l u ing caronamide in a dose of to 3 Gm. ea h 4 hours (Crossen et al. J 134 1o 1947; Sweet et al.: SouthMJ 41 320 1948)

Pure preparation are now available in quantity Penicill n G wa synthesized b du Vigneaud et al. (Sc 104: 431 1946) Appl cation f gauze sopped in culture fl id of *P. notatum* are isolat though interest g a w ll a curat ve in their time (Robinson and Wallace: Sc 98 329 1943) Urticaria, commonl provoked by oral administration and less commonl b parenteral is till frequent nowada s (see Dermatit medicamentosa) Consequ ntial iat xeat on ha been reported only rarely even from huge doses. Yet the effect of all rgic rea tion are oft n deed u pleasant n l sometimes force the discon tin ance of the drug Some persons intolerant to penicillin G will tolerat penicillin O (Vol n t al J 143 14 1950) Penic llin h caused f talit presumabl a aph l c ti

Penicillin i relati l saf wh le sulfonamides re less so. Ther is l ttle the latt can do that the former cannot do well or better xcept to penetrat into the cerebrospinal flui l. Thi fact is not significant with respect to syphil of the central nervous system in which penicill n i known to be curat e despit t fa lure t enter the cerebro p nal fl l Yet penicillin losing popula ty for tetrac line a safer drug and w th few exception at len t a ffects

Penicillin is effecti in syphil yaw p nta, gonorrh a, meningitis (where sulfonamides are preferable) almost all streptococcic fection most taphylococcic infections anthrax, d phtheria, Vincent s d sease nfect e exfoliat e dermatitis nd some cases of erysipel and actinomycos s. Topically it effect i superficial. While a thimbleful of ointment contain g 500 n t per gram often suffices to cure impetigo, i fection eczematoi l dermatitis requires parenteral an l often high dosage

Penicillin not effectual in pemphigus psoria l erythema multiforme lichen planus, lupu erythem tosus, t berculoi bl stomycosi tinea, acne scabies urticaria, contact dermat t (unless seco darily infected, which is freque tly th case) an l a multitude of ther illnesses When focal infect on causes persistent derm titi usually acral, the effect f penic ll n f temporary benefit onl

It ar entifically desirable to te t the sen itivit of orga m cultured from a patient t penic ll n in tro, but cl n cal results do not i variabl parallel the findings The practit oner l k l to cure an infect on before th laborat ry re ders report Because f peci x ret n, t used to be necessary to gi e penic lli ea h 3 hours Practit oners k ow th t many a patient has gott w ll whe supplied with a vial of solut on a syringe an l needles and instruction t tick t i to himself in a lounge f 20,000 to 50,000 units 3 to 3 t mes 4 hours Th oil emulsion of 300,000 un t gi e d l i a practical and advant geou proced re Preparatio ffect f more th 4 hours ha been developed (Sullivan et al Sc 10 10 1 4 An ject on f procaine penicill n G w th alum num monostearat ma ield ffect blood le els for 96 hours

Oral dministrat on is effecti e dosage is seful in i fa t to whose f rmulas penicillin ma be added dequat dosage Tetra line is pref rabl

Sulfonamid and penicillin m be given simultaneousl somet mes t advantage for the former act by bacteriost s and the latte bactericidal especially at the time of cell divis on (Hobby and Dawson JBact 51 447 1946)

Intolerance f penic ll n is commo place (see Dermat t medicamentosa) and the hemical hould be reserved f use wh it i nd cated nd necess ry Sal e solution f crystall peni llin G seems les ften provocat f rashes than the o l emulsion. O e looks at patient feet before st rt g the hemical and tri t avo d it use if tinea present (see Morginson J 132 915, 1946) Failures n therapy w th penicillin are often due not onl to tolera ce but also t th fact that the para te i sensitive to it, a phenomenon noted not long fter the drug first bec me a lable and of p ogressivel greate i cidence d sign fi ce l onl it use a rule cept in the treatment of syph l s

Wh le topicall the drug ha been sed d st g pow ler l f spra as well as in oi tment h les t now seldom sed f local ppl cat because primary irrit t on d sen tiz t on are l k l compl cat ns

Loc l nject ons of penicill n h gh co centrat on in the immediate vicinity of an infection such as a carbu le ha e been highl recommended (K pl n and Rabin AnnSurg 127 1207 1948) but this is not common pract ce a d to my way of thinking possesses little virtue.

Chemistry of Penicillin: Clark et al., OSRD and Med. Res. Council Monograph, Princeton U. Press, 1949
Cohen, T. M., and Pfaff, R. O.: ADS 51: 172, 1945 (miscellaneous skin cases)
Davies, J. W. T., et al.: QJM 14: 183, 1945 (aqueous spray 1,000 U./cc.)
Franks, A. G., et al.: ADS 52: 14, 1945 (topical and intramuscular)
Gerber, I. L., et al.: J 130: 761, 1946 (booster doses to reach foci)
Goldberg, L. C.: ADS 52: 181, 1945 (topical, 500 U./Gm.)
Gyorgy, P., et al.: PaMJ 49: 469, 1946 (oral)
Hopkins and Yeager: J 155: 1206, 1954 (long-acting compound, benzathine penicillin G)
Hellier, F. F., and Hodgson, G. A.: Lancet 2: 482, 1945 (spray, 200-500 U./Gm.)
Keefer, C. S., and Anderson, D. G.: Penicillin in the Treatment of Infections, Oxford Univ. Press, 1948.
Morrison, W. J.: SMJ 38: 320, 1945 (miscellaneous skin infections; Vincent's)
Penicillin-Resistant Staphylococci: Edit.: J 145: 1204, 1951
Richards, A. N.: J 122: 235, 1943 (valuable review)
Romansky, M. J., et al.: J 128: 404, 1945 (Seitz filtered, autoclaved peanut oil 96.0 per cent by volume; gauze filtered, autoclaved beeswax 4.0 per cent; calcium penicillin 100,000 U./cc. of vehicle blended mechanically. One dose 300,000 units per 24 hours, prolonged absorption; no local sequelae)
Roxburgh, I. A., et al.: BMJ 1: 524, 1944 (miscellaneous)
Syphilis Penicillin in: J 130: 677, 683, 688, 694, 696, 1946 (action on T. pallidum; pregnancy; congenital; early; cerebrospinal). See Syphilis, treatment.
Taylor, P. H., and Hughes, K. E. A.: BMJ 1: 603, 1944 (spray 1,000 U./cc.)
Templeton, H. J., et al.: ADS 51: 285, 1945 (local use valuable only in superficial disease)

Polymyxin.—Sterile filtrates of cultures of *Bacillus polymyxa* were found inhibitory to certain gram-negative organisms by Benedict and Langlykke (JBact 54: 4, 1947) and independently by Stansly et al. (BullJHH 81: 43, 1947). Whether aerosporin obtained by Ainsworth et al. (Nature 160: 263, 1947) from cultures of *Bacillus aerosporus* Greer, is identical with polymyxin has been argued (Brownlee and Bushby: Lancet 1: 127, 1948) but the activities are similar. According to the Council on Pharmacy and Chemistry (J 150: 1219, 1952) Polymyxin is the generic term employed to designate a series of related antibiotics derived from various strains of the spore-forming soil bacterium, *Bacillus polymyxa* (*B. aerosporus* Greer). The various polymyxins which have been isolated are differentiated by affixing letters of the alphabet which do not necessarily signify the order of isolation: polymyxin A, polymyxin B, etc. Polymyxin B is the least toxic of those adequately studied. Chemically, the polymyxins are basic polypeptides. Polymyxin B contains leucine, threonine, phenylalanine, α,γ-diaminobutyric acid and a fatty acid of empirical formula, $C_9H_{18}O_2$, and has a molecular weight of about 1,000. It is stable as the acid salt polymyxin B sulfate in the dry state; in solution it is stable for extended periods if buffers are added. Alkaline solutions are less stable. The antibiotic is highly effective in vitro against many gram-negative micro-organisms.

Polymyxin is useful in dermatology in inhibiting *Ps. aeruginosa* (Kagan et al.: JLab ClinM 37: 402, 1951) but when given by injection has been known to cause urticarial and maculopapular rashes and itching especially about the mouth. An ointment containing polymyxin and bacitracin is an effective, seldom irritating combination, according to Gastineau and Florestano (ADS 66: 70, 1952). Kile et al. (ADS 68: 296, 1953, and Pass and Rattner (J 155: 1153, 1954)

Streptomycin was isolated by Waksman in 1941 from a soil streptothrix *Actinomyces lavendulae* (Edit.: J 126: 103, 1944). Its utility in tuberculosis has proved such that the Nobel prize in physiology and medicine was granted its discoverer in 1952. Regarding the chemistry of streptomycin and its variants, including dihydrostreptomycin, see Bogen (J 140: 469, 1949), Tuberculosis, treatment, and the monograph on the drug edited by Waksman (Streptomycin: Nature and Practical Applications, Williams and Wilkins, Baltimore, 1949). Dermatologically its useful use is conspicuous in tularemia (Committee Rpt.: J 132: 4, 70, 1946), chancroid and all forms of cutaneous tuberculosis (O'Leary et al.: ADS 55: 222, 1947). It antagonizes *B. proteus* and *Ps. aeruginosa* and it is the antibiotic of choice in granuloma inguinale (Combes et al.: NYSJM 48: 2024, 1948). Topically while it has proved effective, it frequently provokes sensitization, which may be severe (Goldman and Feldman: J 138: 640, 1948) and its ability to incite eczematous dermatitis as well as to damage the eighth nerve makes it somewhat unsatisfactory. Furthermore resistance is likely to develop in the organism under attack. Thus dihydrostreptomycin ointment, 5 mg. per gram, while extremely helpful in many a superficial infection according to Miller et al. (ADS 61: 648, 1950) is especially useful only during brief periods of time. See Waksman (Sc 118: 259, 1953; The Literature on Streptomycin 1944-1952, Rutgers Univ. Press, 1953)

Terramycin (Oxytetracycline) obtained from *Streptomyces rimosus* by Finlay et al. (Sc 111: 85, 1950) is effective against hemolytic staphylococci, streptococci and pneumococci, with a spectrum resembling that of Aureomycin (Bliss et al.: BullJHH 87: 171, 1950). It is given orally or applied topically or both in the management of dermatoses of various kinds, and appears to be quite safe. I have often used it in furunculosis as a bland yet potently antibacterial covering for crusted lesions. Superficial ecramatoid infections are well managed by the ointment which was highly recommended also by Wright and Tschan (AIDS 67: 1-5 1953); also Robinson et al. (SouthMJ 40: 772, 1953). Pfizer stand[illegible] preparations, 1953 [illegible] polymyxin B.

Orally the drug may induce diarrhea and gastroenteritis, accompanied by marked changes in the intestinal flora (Herrold et al.: PSEBMC 23: 183, 1950); see Moniliasis, etiology; and Council Rpt. (J 146: 254, 1951). Aureomycin (chlorotetracycline) and Terramycin (oxytetracycline) are chemically quite similar (J 151: 46, 1953). The chemical structure, uses and dosage were given by N.N.R. (J 151: 1291, 1953)

Terramycin may be applied topically and given by mouth at the same time safely which is not the case with sulfonamides or penicillin (Tachan and Wright ADS 69: 621 1954) So may Achromycin.

TETRACYCLINE.—See Achromycin. See also Aureomycin and Terramycin.

THIOLUTIN.—See Antifungal antibiotics

TYROTHRICIN is the crude extract from which gramicidin and tyrocidine were subsequently purified. Dubos (JExpM 70: 1; 711 1939) obtained it from a spore bearing soil organism later identified as Bacillus brevis. Toxic when given parenterally causing hemolysis, tyrothricin has considerable usefulness when applied topically in the treatment of infections with gram positive bacteria (Anderson; AD&S 53; 90 1946). Wet dressings rather than ointment vehicles were preferred by Anderson but Fisher and Lee (AD&S 53; 201 1946) pointed out that ointment bases do not lose their effect but rather interfere with diffusion of the drug. MacKee et al. (JID 7 1 5 1946) tested an intra-cerebral solution of tyrothricin in various dermatoses and found it nonirritating soothing and helpful in many cases such as eczema, impetigo and infectious eczematoid dermatitis. It is also used for chronic ulcers where it seems to stimulate tissue growth (Robinson AmJSurg 63 201 1944) Spectrocin combines neomycin and gramicidin in an ointment of considerable value. Tyrothricin containing tyrocidine gramicidin and lanolin was thought by Miller et al. (AD&S 69 303, 1953) to be no great improvement upon an ointment containing any one of the antibiotics singly.

Antihistamine Agents.—Benadryl, Pyribenzamine, Chlor-Trimeton and others have been introduced in the past few years and are notably effective in palliating urticaria, asthma and hay fever. See Council Report (J 132 702, 1946) Epstein (WiscMJ 45 459 1946) O'Leary and Farber (J 134; 1010 1947) Osborne et al. (AD&S 55 309 1947) Acute urticaria is particularly well relieved, and most cases of chronic urticaria are helped. Physical allergy, drug eruption and serum sickness with urticarial manifestation are relieved. Other itchy dermatoses, contact dermatitis, dermatitis herpetiformis, lichen planus and the like are sometimes palliated. Intolerance phenomena occur. See Dermatitis medicamentosa.

Benadryl, β dimethylaminoethyl benzhydryl ether hydrochloride is a white crystalline water-soluble synthetic antispasmodic (Shaffer et al.; AD&S 5 13 1945 Curtis and Owen AD&S 5 39 1945) The chemical composition of several such medicines was given by Waldbott (J 135; 207 1947) The history of their development was clearly outlined by Waldbott et al. (AD&S 61; 201 1950). After Dale and Laidlaw (JPhys 41; 318 1910) showed that symptoms of anaphylaxis resembled the pharmacologic effects of histamine Lewis propounded the theory that allergen unites with antibody in the shock organ and results in the liberation of a histamine-like substance. Bovet and Staub (Compt rend Soc biol 124 547 1937) searched for and found compounds which were antagonistic to histamine. What they first obtained was too toxic for human therapy but researches by Bovet, Halpern, Loew, Mayer and others yielded a succession of practical results (Loew et al. JPh&ExpT 83 120 1945, Benadryl; Mayer et al. Sci 102 93, 1945 Pyribenzamine) In addition to being histamine antagonists, the compounds were shown to have procaine-like effects by Leavitt and Code (PhExpT 85 33, 1947) and much work followed on the topical application of antihistamine drugs in the relief of pruritus. See also Dale (BMJ 2 281 1948)

The antihistamine effectiveness of a chemical compound may be tested by iontophoresis of histamine (Perry et al.; JID 11 461 1948) Iontophoresis of the antihistaminic was tried as a method of treatment of pruritic dermatoses by Aaron et al. (JID 10 85, 1948) See also Sternberg et al. (J 14 960 1950)

Antihistamine drugs are generally given by mouth. Chlor-Trimeton may be one of the best, being effective, adequately enduring in its effect for six to eight hours, and provoking a minimum of side effects as a rule. Benadryl is frequently sedative and this is an advantage in some patients, especially for the evening dose of medication, and for hyperpyrexia. Intravenous injection of antihistamines is admissible but seldom desirable.

Topical therapy with antihistamines yields, in dogmatic generality, more harm than good. They are often irritants. They spread undiagnosed bacterial dermatitis. They seldom accomplish what cannot be done better by other modes of topical treatment. Yet Perazil Cream has its virtues in chronic lichenoid dermatitis when this is dry and stabilized. I advise strongly against the topical use of antihistamine drugs on moist dermatoses and poison ivy.

See Feinberg and Bernstein (J 13 3 4 1947) Pyribenzamine ointment, Sulzberger et al. (JID 10 41 1948) Pyribenzamine cream; Shelmire (PostgradM 4 442, 1948) Thephorin ointment; Ellis and Hu dick (JID 11 25 1948) Thephorin often irritated or sensitized; Epstein and Macaulay (JID 12 145 1949) Histadyl cream; Inman and Cow (BMJ 1 1944, 1952), potent sensitizers; Overton (BMJ 1 874, 1948) Antistine; Lea et al. (JPh&ExpT 90 22, 1947) Histadyl; Pillsbury et al. (JID 11 435, 1948) Hydrillin; Spielman (NYSJM 48 2297 1948); Perazil; Kierland and Potter (PSMMC 23 48 1948) Thenylene; Keeton and Sheard (JID 9 65, 1947) Thephorin. Council on Pharmacy and Chemistry (J 143 144 1953), omission of dermatologic preparations of antihistamines from N.N.R. Warin (BMJ 1 1946, 1954) drugs available in England, usefulness mainly limited to urticaria, ill effects.

Antimony.—Various compounds containing antimony have proved efficient in treating granuloma inguinale, leishmaniasis and creeping eruption (q.v.). Fuadin is a valuable preparation of trivalent antimony. It is said to help in mycosis fungoides (q.v.)

Antipruritics.—Phenol is the most reliable antipruritic, in a strength of from 0.5 to 2%. Menthol evokes a sensation of coldness. Some synthetic topical anesthetics, such as Orthoform and Cycloform, prove serviceable at times. Ethyl aminobenzoate (Anesthesin) in 2 to 3% strength is helpful in combating intolerable itching. The control of itching receives detailed consideration in the chapter devoted to pruritus (q.v.). Among the things worth doing in brief are elimination of the stimulating effect of caffeine, administration of sedatives like aspirin, chloral hydrate or phenobarbital, rarely opiates; and protection of denuded, raw nerve ends by means of cool, bland poultices, which raise the local humidity to 100%, constrict the dilated vessels and cool the inflamed skin. The topical use of antihistamine chemicals is rarely to be advised (see Antihistamine agents). Benadryl has useful sedative as well as antipruritic effects.

Antiseptics.—A wide assortment of chemicals designed to destroy pathogenic organisms is available (see Livingood and Mullins: PostgradM 12: 16 1952). Phenol, the classic one, is used by dermatologists mainly for its antipruritic properties. Several antiseptics receive in this chapter paragraphs of their own, such as gentian violet, iodine, sulfur and Vioform. Numerous antibiotics (q.v.) serve so well when applied topically that other types of antiparasitic agents are considerably less popular than in former days. The phenyl mercuric compounds, potent against fungus infections in vitro, are strongly irritating even in low concentration and a practitioner is not likely to use them, although they have their advocates (Byrne: BMJ 1: 90 1947). Mercuric bichloride 1:10,000 aqueous solution, is good for soaks or poultices if tolerated. Ammoniated mercury (the U.S. Pharmacopoeia preparation being 5%) is an old friend, still a good remedy for impetigo, more often used in the treatment of psoriasis. The combination of ammoniated mercury with salicylic acid, which enhances the potentiality for irritation, was studied by Siemens and Schreiber (abs YBD 1946, p. 190); an ointment containing 5% each may cure a stubborn case of rosacea like folliculitis after other efforts have failed, as Staley showed us. Merthiolate and Mercresin are serviceable liquid antiseptics, although they are frequently irritating when applied in an ointment vehicle (see J 137: 780, 1948). Oxidizing antiseptics include potassium permanganate, which, in a concentration of 3 grains or somewhat less to the gallon of water, is invaluable in treating chronic lichenoid dermatitis of the legs, stasis dermatitis, poison ivy, various vulvovaginal infections and irritations, and infectious eczematoid dermatitis. Hydrogen peroxide and sodium perborate are of value as mouth washes, but are capable of irritation. Meleney's zinc peroxide has been highly recommended in the management of anaerobic streptococcic ulcers. Urea peroxide was deemed valuable by Tharman and Brown (JID 8: 11 1947; ADS 55: 801 1947). Sharlit (NYSJM 46: 147 1946) reported on a study of ozonides, which are organic peroxides made from ozone and unsaturated fatty acids, releasing nascent oxygen. Quaternary ammonium germicides, surface active agents comprising a class of amines in which the nitrogen has a covalence of 5, include such antiseptics as Zephiran, Phemerol and Ceepryn. They have practical surgical and industrial disinfecting uses. Being wetting agents, they abet débridement and are especially suitable for soaks and moist compresses; see Blank and Coolidge (JID 15: 249 1950). The nitrofurans have been popular (Downing et al.: J 133: 299 1947), notably with plastic surgeons, but Furacin often sensitizes (Downing and Brecker: NEngJM 239: 862 1948). The flavine antiseptics to which Strept. pyogenes is susceptible and Ps. pyocyaneus is not are effective even in the presence of blood serum (Edit.: BMJ 1: 837 1933). The aminoacridine compounds have won popularity in managing wounds, but can retard healing if too concentrated (Brown et al.: BMJ 1: 241 1953). Fatty acid antiseptics have their use in treating mycotic infection (Theodore: J 143: 226 1950); see Tinea, treatment.

See Reddish (Antiseptics, Disinfectants, Fungicides and Chemical and Physical Sterilization, Lea and Febiger 1954).

Dyes.—Gentian violet, a pararosaniline dye (pyoktanin blue is an old proprietary name for this) and the closely related methyl violet and crystal violet are deeply staining, nonirritant, nontoxic substances which evince especial affinity for gram-positive parasites. Available inexpensively in crystalline form, gentian violet is soluble in water, alcohol and chloroform but insoluble in petroleum fractions. It is an excellent parasiticidal local application (Sutton: J 110: 1733 1938). Acriflavine, brilliant green, carbol fuchsin and scarlet red are also valuable antiseptic dyes.

Arsenic, when prescribed in the form of liquor potassii arsenitis, sodium cacodylate, or arsenious acid, is largely excreted by exfoliation, for it becomes attached to epithelial tissue. When given over long periods of time even in small doses, arsenic may cause pigmentation and arsenical keratoses. See Dermatitis medicamentosa.

SODIUM CACODYLATE (sodium dimethylarsenate) is worthless as a spirocheticide but is useful in dermatitis herpetiformis.

ARSPHENAMINES.—Many possess specific treponemicidal properties. Chief among these are arsphenamine, neoarsphenamine, sulfarsphenamine, Bismarsen, acetarsone and Mapharsen. The object in compounding the agent is to secure a preparation of maximum injurious effect on the invading organism and minimum ill effect on the host. These are tonic in many disorders as well as efficient in the treatment of syphilis (q.v.). Toxicology is discussed under Dermatitis medicamentosa (q.v.).

Atabrine.—See Lupus erythematosus, discoid, treatment.

Aureomycin.—See Antibiotics.

Autogenous Serum.—For autohemotherapy some 10 cc of blood from the cubital vein is reinjected at once intramuscularly. Or serum after centrifugation may be used in place of the whole blood. From 3 to 10 injections are given at intervals of from 3 to 5 days. Various dermatoses may be treated in this way though the *value of the method is doubtful.* Autohemotherapy is followed by a fall in the number of circulating eosinophils, an effect like that of ACTH of seeming to stimulate the adrenocortical tissue (Sauer: JID 16: 1 1951); but no such effect was found by Franksen and Rasmussen-Jensen (Acta allergol 8: 6 1955). *I am hard up for something to do when I use autohemotherapy.*

Bacitracin.—See Antibiotics.

Bacteriophage.—Interest in this phenomenon from the therapeutic standpoint has *practically disappeared, for phage may be judged to have failed* (Edit.: BMJ 826 1951). Combes (NYStJM 4 : 1143 194) reported on the use of various filtrates on various skin infections. See Krueger and Scribner (J 116: 2160 2209 1941).

BAL, British Anti Lewisite, *2,3 dimercaptopropanol, is a dithiol which reactivates an* arsenic-inhibited pyruvate oxidase system and so detoxifies trivalent arsenical poisoning as well as poisonings with other heavy metals. Its administration is followed by marked increase of arsenic excretion in the urine. The 10% oil solution is injected intramuscularly *each 4 hours for 4 doses of 0.5 cc./50 pound body weight.* Toxic reaction may occur but are preferable to arsenical encephalitis or dermatitis, which BAL may cure. See Peters (Nature Nov. 3 1945); Waters and Stock (Sc 102: 601 1945); WJTDM 101 104 (Oct. 1944); Sulzberger and Baer (J 133: 293, 1947). *BAL is often effective in mercury* and gold intoxication as well as in arsenical dermatitis, *encephalitis and optic atrophy* while it appears to increase rather than diminish the toxic effect of lead (Longcope and Luetscher: AnnIntM 31 545 1949). It has been tried in chrome dermatitis (q.v.).

Baths.—See Cleansing.

Benadryl.—See Antihistamine Agents.

Bismuth causes the rapid disappearance of the spirochetes from primary and secondary syphilitic lesions. *It is generally* inferior in its *therapeutic properties to mercury. It* cannot be relied on as the sole antisyphilitic drug (Walsh and Becke: J 116: 494 1941). Bismuth is also used in the treatment of lichen planus, lupus erythematosus and warts (q.v.). While the subsalicylate in oil suspension is the usual preparation Thiobismol and Bismarsen (Beerman et al.: J 170 333, 194) have also been popular.

Bismuth compounds which differ in solubility differ in rapidity of absorption and excretion and in duration of action. If continued action is desirable too rapid absorption *would necessitate frequent injections, and slow absorption might delay the effect and tend* to produce cumulative toxicity. Oil-suspended bismuth subsalicylate shows slow but continued absorption. Most of the clinical toxic symptoms, including stomatitis, dermatoses and nephrosis, occurred with this preparation (Cole et al.: AmJS 23: 143, 1939).

The usefulness of a bismuth preparation involves the concentration of active bismuth in the tissues and the height, course, rise, duration and decline of this concentration. The more prompt absorption of the watery solution tends to remove them from the site of injection and to empty the absorption deposit so that the concentration of bismuth is not maintained with weekly administration. Oil solutions are easier than similar to watery solution in their absorption but the difference in practice because they are injected in higher doses, so that weekly injections suffice to produce high and lasting absorption. It is therefore not necessary to inject them more often than weekly. Additional advantages of the fact that they usually produce less local irritation than watery solutions. For its use in syphilis see Syphilis, treatment.

Toxicity and tolerance depend on the content of element bismuth and its rate of reaching the blood, so that intravenous administration is dangerous (Clausen: JPhExpT 6 338 194).

Sobisminol mass and its trimate for oral administration are also used in therapeutically active concentration. *Lacking the dangers of injections, they have great utility* (Kay and Fricke: CalWM 50 349 1939; Howles: SouthMJ 41 1032, 1948; Miller and Delane: ADS 60 106, 1949).

Boric Acid is useful because its saturated solution, 3% or so, is isotonic and bland. Its antiseptic power is probably slight but it is seldom harmful. If through error boric acid solution is fed to a baby the result is catastrophe, for it is poisonous (Young et al.: CanadMAJ 61 447 1949). A teaspoon in a pint of water makes a solution to be poured *on a towel, which is laid on a dermatitis such as sunburn or wrapped about the fingers in* dermatitis of the hands, supplying coolness, high humidity and comfort. Boric acid ointment has caused fatal poisoning from percutaneous absorption (Watson: J 129 332, 1945). See Dermatitis medicamentosa.

Calcium.—Coagulability of the blood is perhaps diminished in a number of cutaneous disorders, particularly urticaria, pernio, pruritus and purpura (Tobias: JID 10 229 1948) and calcium salts may be given to overcome this deficiency. Seldom indeed have *I seen benefit resulting from their use either by mouth or intravenously* although intravenous calcium seems really helpful in the cases of penicillin allergy characterized by a rash resembling erythema nodosum.

Carbomycin.—See Antibiotics.

Cathartics.—*Saline laxatives are usually to be preferred. Magnesium sulfate is less* palatable than magnesium citrate. Milk of magnesia (N.F. II) is effective. Aromatic fluid extract of cascara sagrada practically never causes a rash. Mineral oil and the more elegant

proprietaries are usef l. Calom l (gr 1 ll) is drastic but effective. Bad bowel habits, fatigue and hypothyroidism ar among the common causes of constipation. Many patients may ad antageously increase th rati of fruit and vegetables in their diets. One may give the advice t go to bed earlier get p earlier an l allow a q arter hour of leisure in the morni g for evolution of an urge t stool; also, missing a day l rarely f tal.

Chloramphenicol.—See Antibiotics, Chl romycetl

Chloromycetin.—See Antibiotics.

Chlorophyll solution and ointment had a vogue. The preparations were nonirritating and were alleged to possess healing properties (Boehringer: Praxi 32: 703, 1943). Water soluble chlorophyll relieved symptom and alle iated a umber of recalcit nt dermatoses in patients of Langley and Morgan (PaMJ 51: 44 1947). Zeligman (JID 13 111 1949) reviewed the literature and commended the effect of the oi tment in treati g sta i der matitis. It seems to be deodorant (Council Report: J 140: 1330 1949).

Chloroquine.—See Lupu erythematosu discoi l, treatment.

Chlor Trimeton.—See A tihi tamine Agents.

Chrysarobin.—See Reducing Substances.

Clavicin.—See Antibiotics, antifungal.

Cleansing.—The tepid water bath with a mild soap is excellent. Soap baths accomplish débridement, and in dermatology are prescribed with det iled instruction as other medi ci es are. They are necessary in scabies to enable para iticidal agents to get at the mites, and the average case of tinea of the feet ca be cured by lev ti n aeration and the proper use of soap for the removal of excess corneum. Soap m st be rinsed off thoroughly. The typical hospital bath i flicted upon bed patients with wa hrag and a small basi of water causes much irritation.

Saturated fatty acids of low molecular weight more often gi e positive patch test than those of higher molecular weight. Reaction to castor oil is rare. Irritation by soaps i not directly related either to the lkalinity or the fatty acid component alo e. Some fatty acids at pH 7 are more irritant than others at pH 5. A detergent composed of 25% sulfonated oil, 25% liquid petrolatum and 50% water at pH 6.5 proved cellent in replacing soap, and relapse of dermatitis occurred when th use of soap wa resumed, as reported by Blank (ADS 39: 811 1939); see also Lane an l Blank (J 118: 804 1942).

Cationic soap is the t rm applied to germicidal and c eansing detergents i about 1% aqueous conce tration (J L 4 09 1944). They leave an imperceptible yet strongly germicidal film on the skin, and may be of some use (Miller et al.: PSExpB 54 1 4 1943).

All soaps are alkaline. Si ce alkali tends to c use dissol tion of epidermal cells, soaps are contraindicated in acute dermatitis, especially eczematou (Pa khurst: ADS 43 89, 1941). Highly alkaline soap, such as sapo viridis, may be desired f r it keratolytic effect in psoriasis, seborrheic dermatitis or acne. Medicated soaps possess little added germicidal value and are frequently i ritating (J 1 4 1193 1944).

Scales and crusts may be removed b means of mineral l, st rch poultices, or benzine, which is effecti e for cleansing oily greasy surfaces and removing adhesive plaster.

Baths in plain water may dilute and rinse away contactant irritants. They are sel dom harmful, though patients must be cautioned not to rub their skins while immersed. The temperature is important and should generally be t pid or cool as judged by the pa tient when a soothing, antipruritic effect is sought. Baths can spread pathogenic orga isms over the skin, but the shower bath seems rather to get rid of bacteria than to spread them.

The med cated bath is the means for getting a medicine all over a patient when t is easier to put the pat ent i to the medicine than to put the medicine on th patient because of the extent of his dermatosis. Aluminum acetate, a tablespoon to the tub is a common prescription of mine in po son ivy extensive and itchy pityria i rosea and widespread contact dermatitis. The conti uous bath has a place in the treatment of pemphigus a d of burns (Riehl: J 94: 1058 1930). The starch bath, as recomme ded by Swe tre is made by cooking 2 cups of cornstarch (not laundry starch, which contains borax) until soft and adding this, with a cup of baking soda, to the tub of water at comfortable temperature.

The potassium permanganate bath has great utility in ntoeczematization dermatitis and fectious eczematoid derm titis, using ten 5-grain tablets to 15 gallons. It is u tidy i the home but indispensable in managing many a hospitalized patient. Proportionately smalle quantities may be made up for soaking an arm o leg the hands or feet, or as a douch i the treatment of mycotic vaginitis with prurit vulvae.

Soda baths and tar baths are sometimes employed n th t eatment of psoriasis and chronic dermatitis.

The oatmeal bath is often soothi g and comforting in widespread dermatiti or urti caria. A cup of oatmeal bo led to a jelly is poured to a cloth sac ove the drawn tub of water at 100 F. The sack is tied t ghtly and sq eezed about in the water; it prove ts the oatmeal from stopping the plumbing.

Bichloride of mercury, 1 12,000 (3 Gm or 10 f the Large Poison Tablets [U.S.P.] in 15 measured gallons of water) provides valuable though somewhat hazardou a tiseptic and astringent bath useful in widespread i fect ous dermatitis. One must learn how to use and when to stop such baths. Absorption when the epidermis is much eroded results in mercurialism, with diarrhea or worse, d many a skin does not tolerate mercury at all.

Cod-Liver Oil.—Externally used thi sub tance has received favorable reports in the treatment of burn (Council Report: J 1 1: 59 1943) It is soothing and protective may be somewhat be t rucidal (*Lichten telu: Lancet* : 10_3, 1939) and ma contribut some local ben fits of vitamin A.

Diets.—Correct and adequate nutrition is necessary in dealing with dermatologic patients, as it i in managi g illnesses of any kind. Especially in chronic lichenifying d rmatitis I have been impressed with the need for a high prot in liet ((Gay: ADS 61: 901 1950) II poprot inosis wa intelligently discussed from the dermatological stand point l y Lynch and Sul elv (J 147: 115, 10 1)

Di tary restriction i infantile ecr ma frequently produce malnutrition and in man aging this disease where restri tions based on skin allergy test are so commonly futile I believe in feedi g the bal y so that at lea t it does not it h on an mpty stomach. A di tary rror I correct almost daily i the overingestion of c ff in, which ma ks fatigu a d increases irritability

Diet tic is a larg sul ject fo a mall paragraph but the nutritional a pects of ma y dermatoses re discussed under treatm nt of individual diseases and in the section on metabolic dermatoses including avit minoses.

It is seldom in leed that a skin disease is in fact caused l y a food, a compared with the frequency with which f od allergy i imagined especiall by pediatricians, t be the *cause of an eruption.*

Un aturated fat in the form of lard gi n in large amounts, h lped a number of chronically eczemat u patient of F nerud et L (ADS 44 840 1941)

Di ting f r obesity often concern the dermatologist in man ging dermatitis of the legs. Extra riboflavin may h lp sebo rheic I rmatiti (q.v) and psoriasis. Many a pa tient with a n need supplementary iro and vitamin therapy and in this condition I have stressed the utility f the low fat li t restricting especially milk and butt rf t a a mea s for dimini hing the activity of sebaceous glands. See Avitaminosis; Starvation edema; Stomatit f ut itional lehency; Lichen h omimu mplex

Diuretics.— A dermat logi t seldom prescribes a i reti but occ nally th e trem welling f th low r extremities which may company sev re d rmatitis will respond fav rabl to the injection f 1 0 cc M re hydrin or t Neohydrin tablets.

Dusting Powders generally con i t in the main of corn tarch zinc oxide zinc stearat alamin and boric acid

R	Zinc xide Zinc stearat T lc	of each t 60.0
Sig	*Bland dusting powde*	

On may ad l antipru itic or ant eptic hem cals to this ach a camphor, 2.0 grams. Desen x pow l r coat i ing zin undecyll at a d undec linic acid, is usef l in the treat ment f t nea ped (q.v) The absorpti e property f pow l rs w st died l y R (JID 6? 310 1950)

Ephedrine ha pharm cologic prope ties imilar to epi ephrine but the d rat on of the ffect s relatively prolonged, and it i act e when gi en by mouth

Epinephrine, a potent vasoconstricto palliates rt caria (Welch J 116 2390 1941)

Erythromycin.—See Antibiot cs.

Ethylene Disulfonate deserves ment on because of the interest ng controversy re gard ng ts x te e G en intramuscularly a expensive preparation is dosed accord g t a compl x r tual nd is alleged to be fit many kinds of allerg disease Ketch m (JMoSMA 45 896 1948) i a beli ver and Bartlett (MRec 160: 467 194) reviewing 1500 cases so treated reached f vorable conclusions. The Council on Pharmacy (J 131: 1493 1502, 1946) f und the prod ct indisti guishable from pure d st lled water Th con t nued sale of this remedy on the ba is f ava lable evidence is an insult to the intelligence of ph si ans.

Foreign Protein, in the form of typho d or other vaccines, and various oth sub stances somet mes y eld benefit n a manu all derstood in psoriasis, urticaria, pruritus, and dermat ti f nknown cause Foreign protei therapy i dangerous and often harm ful n lupu erythematosus d pemph gu (Cec l an l Hektoen: J 10_ 1705 1846 1935) *Nonspec fic prot* therap recei ed appro l of W right (ADS 23 115 1931) who com mended njection of milk n f runculosis and idiopathic pruritus. See syphilis, treatment with fe e Piromen, a f ver inducing polysaccharide s thought by some authorities to have alterat e p ope t es seful a wide assortm nt of recalcitra t ailments of obscure cause (Kierland and Kulwin ADS 62 571 1950)

Gold preparations, especially gold sodium thiosulfate have been found useful in dermatology *Lupu erythematosu (q.v)* d cert n t bercul d m y respo d favorably Gold injections re dangerous see Dermatitis medic mentosa. I seldom use them.

Gramicidin.—See A tibiotics, Tyrothricin.

Health Resorts.—See Cipollaro (J 134 249 1947)

Histadyl.—See Antihistam ne Agents.

Histaminase, available as Torantil, is an enzyme wh ch destroys histamin the tox c substance thought responsibl fo anaphylactic responses. *Perhaps it has value in serum* sickness and hi es (Laymon and Cumming JID 301 1939)

Hydrillin.—See Antihistamine Agents.

Ilotycin.—See Antibiotics, Erythromycin.

Iodine and the Iodides internally are used in sporotrichosis, blastomycosis and actinomycosis. Iodides are not spirochetIcidal. Th potassium salt i given by mouth the sodium salt intravenously By now iodides have been retired from exhibition in the treatm nt of syphilis, but in this connection are of historical interest Topicall iodine is a valuable antiseptic (Nye J 108: 50 1937) being as effective a anythi g available against *Ps. aeruginosa* which is a difficult parasite to handle, even with antibiotics. In an occasional allergic patient iodine applied to th skin vesiculates. Iodides often cause dermatiti medicamentosa (q v)

Iron is of dermatologic value mainly for sore tongue due to secondary anemia. Patients with acne and oth r chronic dermatoses often need it See Haden (J 111: 1059 1938); Hall (J 151: 1 1953)

Keratolytics are agents for dissolving the corneum. Salicylic acid resorcinol, and alkalies are of this class. The keratolytic action of soaps is due to alkali. These fi d their usefulness in hyperkerat tic condition such as scaly tinea.

Lipocaic, Dragstedt s pancreatic xtract which diminI hes cholesteremia and aids fat metabol sm, ha been alleged to help psoria is, but seem to me dermatologically val les (Rewlett and De Kay: RockyMtMJ 3 : 347 1940 Wal h: JID 4: 50 1941)

Liver Extracts have thei place in treatment of dermal manifest tio of certain *anemias and avitaminoses. Their preparation was clarified by Teeter (J 1 7 973, 1945)* They are used in hepatic deficiencies and some int xication such as arse ical dermatitis (R ssell RJD 60: 378 1948)

Local Applications employed in dermatology can be classed a to form of application and pharmacologic purpose. Remedial agents may be prescribed in the form of baths, compresses, dressings, lotio s, oi tments, pastes, pow ders or plasters Their purposes are cleansing, soothing protective stri gent antipruritic antiseptic keratolytic, reducing stimulating e escharotic. Physical agents as well a medicaments are used.

Lotions.—Relief of irritability is often accomplished by moist dressings intended t exclude air by mild astringe ts, or by lotions. In oozing itchi g dermatoses, wet dressings of aluminum acetate (a level teaspoonful to the quart of water) or pot ssium permanganate (1 grain to the pint of wat r) offer con iderable immediate relief.

Burow s solution of aluminum acetate has long been a popular astringent lotion in the treatment of burns and oozing dermatoses. A useful modification is:

R	Aluminum sulf te	5 0
	Lead cetate	25 0
	Water	500 0
Sig.	Astringent lotion dilut as requ red t avoid irrita t effect.	

Boric acid and liquor alumi um acetate together were commended by Vörner (MünchMWchr 51: 1000 1903)

Goulard s extract (20% lead acetate in water) when diluted 1:50 is good in moist compresses.

Dalibour water i anothe astringe t im lari used (Anderson SouthwestM 23: 330, 1939; Riordan et al.: NYSJM 43 802, 194)

R	Coppe sulfate	1 0
	Zinc sulfate	5.0
	Camphor water	to 240.0
Sig	One teaspoonful to half a pint of water for moist dressings.	

Pick s liniment forms a transluce t jelly which dries as a film

R	Tragacanth	5 0
	Glycerol	5 0
	W ter	100 0
	Mix with grinding	
Sig.	Apply freely to relieve burning a d itching.	

In contact dermatitis on beaut tes to apply ny chemical when it i not k own whether the patie t is susceptible to irritation by it One may appl petroleum jelly and, over that, clean soft towels moistened with cool water, plain or isot nic with t ble salt in it, a dram to the quart. An irritated skin will in a few hours or days return to normal if f rther rrita t cont ct has been prevented and if secondary i fect on does not complicate.

Calamine lotion has a drying effect

R	Phenol	1 0
	Starch	
	Zinc oxide	
	Prepared calamine of each	20 0
	Glycerin	10 0
	W ter t	200 0
Sig.	Carbolized calamine lotion Shake and apply to allay itching.	

Calamine lotion may be modified by the incorporation of various substances such as alcoholic solution of coal tar or 0.05% bichloride of mercury. Bentonite, a clay, may be put in the vehicle though tragacanth is a good. It is common knowledge that calamine zinc oxide contaminated with iron oxide which is harmless. Experimentation with red, brown and black iron oxides will enable one to match a lotion to the complexion on which it is to be applied (Goodman: NYSJM 41: 580 1941).

A good cleansing antipruritic lotion is Pusey's liniment:

R	Phenol	1.2
	Powdered tragacanth	4.0
	Sodium benzoate (as preservative)	0.2
	Olive oil	120.0
	Water	to 480.0

Sig: Soothing lotion. Apply freely to itching.

Magnamycin.—See Antibiotics, Carbomycin.

Mercurials are useful antiseptics (q.v.) and have been thought to be valuable in the treatment of syphilis and lichen planus. The protoiodid by mouth, the salicylate in oil intramuscularly and the ointment for inunction were the common preparations.

Naftalan.—See Tars.

Ointments have a wide sphere of usefulness. They consist of lipids of various kinds, perhaps emulsified, in which divers medicaments are suspended or dissolved. White petrolatum jelly is the common vehicle but is not penetrant. Cholesterolized bases are more penetrating. Lanolin (wool fat) takes up watery solutions and is on that account a useful vehicle. Vanishing creams are watery emulsion composed mainly of higher fatty acids and wetting agent.

Ointments are generally not used if weeping exists. The addition of starch thickens an ointment and enhances its power to take up secretions. Ointments smeared over staphylococci dermatoses are likely to spread the disease.

Rose water ointment is the U.S.P. cold cream.

Many ointment bases are available from proprietaries possessing much elegance. No great advantage accrues from their use except the recognized virtues of a polyethylene glycol Carbowax, which is water-soluble and especially welcome in applying medication to the scalp from which it is easily washed out (Maynard: JID 8: 223 1947; Hopkins JID 7: 1 1 1946). Vehicles, their physical chemical and functional characteristics were discussed by Lane and Blank (ADS 54: 487 650 1946). Those who prescribe compounded vehicles and judge them overrated. See Goodman (ADS 45: 1101 194_; 49: 16 704 1944). In considering a medicament the skin, the vehicle must be bland and it must be compatible with the medicament it holds. Water-miscible bases and oil-in-water emulsions release antiseptics from 50 to 1000 times more effectively than grease bases or water-in-oil emulsions (Zheutlin and Fox: JID 11: 101 1949) but Aureomycin deteriorates in water containing vehicles, while Aureomycin in petrolatum is one of the most practical forms of this topical medicines.

Numerous ointment bases were discussed by Mumford and Mumford (BJD 53: 45, 1941) and by Perrin and Halpern (JID 16: 1951). Various formulas for protective ointment of emulsion type water-in-oil and oil-in-water with or without the use of emulsifying agents were given by Peel (AustralJD 1 1953) who discussed water-soluble and greaseless bases and the pertinent pharmaceutics. Ointment prescription effect and the influence of pH were discussed by Herrmann (BJD 54: 1 194). The types composition and pharmaceutical usefulness of wetting agent were discussed by Nazzaro (Dermatologica 4 185 1953).

Antihistamine Ointments.—See Antihistamine Agent.

Boric Acid Ointment is losing popularity because of its possible toxicity (Pfeiffer et al: J 1 8 768 1945). Cod liver oil ointment possesses no remarkable virtue (see J 121: 39 1944).

Covermark is useful for hiding blemishes even large macular hemangiomas. The formulas of cosmetics of comparable effectiveness were given by Klauder and Gross (ADS 41 744 1940) and Hellman (ADS 57 70 1949).

Sunscreening Preparations for shielding the skin from actinic light, such as Afil, are discussed under Sunburn (q.v.). They are needed in managing Lupus erythematosus (q.v.).

Lassar's Paste contains zinc oxide 25, cornstarch 25, petrolatum 50. To it 1 to 5% salicylic acid is often added, as well as 0.5 to 1% phenol. It is a thick, protective antipruritic substance of considerable utility.

Pelolds (mud etc.) have physical effect of some interest (Slager: J 1 4: 431 1944). Bentonite, hydrated luminum silicate clay, is a detergent and dispersion agent incompatible with acids and inorganic acid salt. It is prescribed by some dermatologists (Goodman: ADS 49 764 1944).

Protective Ointments, while low on the list of preventive measures, are often the only available means of protection. In other instances they protect the skin from irritants which may escape the other preventive measures. The face cannot be covered by protective clothing and often the work must be carried on with bare hands. When a protective ointment is used the worker removes it with soap and water after work and so removes at the same time what ever irritants are on the skin. This adds considerably to the protection supposedly given by the ointment (Schwartz: MCNAm 26 1195 1942, giving type formulas and composition of industrial protective creams and

cleansers) Varieties include vanishing cream facilitating removal of soil when washing invisible glove films which may be water-soluble or water-insoluble fatty water-repellent ointments, ointments containing nonirritant chemicals detoxifying specific irritants, ointments serving as vehicles for inert powders which form protective covering and agents protecting against photosensitization Lanolin and petrolatum afford more secure protective films than other substances and the addition of powders to them diminishes their protective efficiency

Sunscreening ointments are discussed under Sunburn treatment

SURFACE ACTIVE AGENTS for wetting, penetrating, emulsifying dispersing, solubilizing, foaming, and washing have occasioned much dermatologic interest (Speel; JID 6: 293 1945; Dumeling: ADS 43: 764 1941) The molecule of the wetting agent generally contains water-soluble (hydrophilic) and also lipid-soluble (hydrophobic) groups, because of which it becomes oriented at an interface and lowers surface tension. Methods of cleansing and protective applications and formula utilizing some of these were discussed by Klauder et al. (ADS 41: 331 1940) Much industrial dermatitis is caused by cleansing agents. Schwartz (PHRpts 56: 1788 1941) commended sulfonated castor oil 50, vegetable oil 48, and a wetting agent such as Duponol 2, as a soapless cleanser for industrial use. Accepting the utility of cleansers dependent on these for their effectiveness as substitutes for and often improvements upon, soaps, which are common causes of dermatitis, I am nevertheless hesitant to recommend them highly as adjuvants of therapy I am perhaps naively pleased with the results of treatment in which few bases are prescribed other than petrolatum and lanolin. It is true that penetration can be enhanced by the choice of vehicle (MacKee et al.: JID 6: 309 1943 43, 1946) and occasionally this is necessary A typical ongreasy ointment base (Downing et al.: ADS 50: 8 1944) of cosmetic elegance capable of being washed off easily is:

R	Sodium lauryl sulfat	0.8
	Cetyl alcohol	15.0
	Glycerol	8.0
	White petrolatum	14.0
	Water	35.0

ZINC OXIDE OINTMENT (zinc paste) does not absorb water but possesses some antiseptic power (Strakosch: ADS 49 8 1944) An emulsion base may be prescribed however

Neoarsphenamine.—See Arsenic, arsenicals; Syphilis treatment Dermatitis medicamentosa, arsenicals.

Neomycin.—See Antibiotics.

Nystatin.—Antifungal antibiotic; see Moniliasis treatment.

Parathyroid Extract is sometimes useful in calcinosis prurigo and papular urticaria. (Albright: J 117: 527 1941.)

Penicillin.—See Antibiotics.

Perazil.—See Antihistamine Agents.

Pituitary derivatives have been used to encourage the growth of hair Pituitrin may relieve the pain of herpes zoster Compare ACTH and cortisone.

Polymyxin.—See Antibiotics.

Prescriptions are listed in the index.

Pyribenzamine.—See Antihistamine Agents.

Quinacrine.—See Lupus erythematosus discoid treatment

Reducing Substances hasten keratinization and influence favorably such diseases as psoriasis and seborrheic dermatitis. Cornbleet (ADS 33: 625 1936) found the ability to reduce methylene blue greatest in dihydroxyanthranol (Anthralin or Cignolin see J 1 4 647 1944) while in order of diminishing potency were chrysarobin pyrogallol, juniper tar crude coal tar precipitated sulfur coal tar solution and ammoniated mercury

Chrysarobin is a medicine the dermatologic aspirant must learn to use skillfully On the skin it is oxidized to oxychrysarobin, chrysotoxin and chrysophanic acid, the first being therapeutically active and the last not (Strakosch: ADS 49: 1 1944) Petrolatum is the best base, although chloroform is also a vehicle suited to certain purposes. Its application induces erythema followed by peeling, and it is a classic agent in the treatment of psoriasis and dermatomycoses. In the eye which it may reach through misadventure, it provokes violent and hazardous conjunctivitis and keratitis. Hence it is rarely put on the scalp and is prescribed invariably with the warning to keep it from the face. A potent reducing agent, its action is neutralized promptly by potassium permanganate. Chrysarobin conjunctivitis treated with frequently repeated washes of the antidotal 1 5,000 $KMnO_4$ and cortisone eyedrops is not the fearsome complication it has been thought to be. A sophisticated patient can use it on the scalp safely

Resorcinol, meta-dihydroxybenzene is as useful as salicylic acid and similar in its properties. Its action is keratolytic and irritant (Strakosch: ADS 48: 393, 1943) It stains blond hair reddish. Euresol, a proprietary resorcinol monoacetate is often prescribed in a lotion for dandruff

Salicylic Acid, hydroxybenzoic acid, has the property of separating, swelling, and macerating keratinized epithelium. It is a useful antiparasitic substance. It is antipruritic in from 1 to 2% concentration in an ointment. An alcoholic solution is frequently prescribed in seborrheic dermatitis and tinea. As an active ingredient in Lassar's paste,

it serves as an antipruritic and keratolytic medicament effectual in an assortment of conditions. Salicylic acid reinforces the action of sulfur. On corns 40% plasters may be used. See Goodman (ADS 54: 6[illegible], 1946); Strakosch (ADS 4[illegible]: 16, 1943).

Salicylates.—Aspirin is a valuable sedative and analgesic.

Sedatives.—Opium is of little value as a rule in diseases of the skin. It frequently increases pruritus. Bromides are not satisfactory, being prone to intoxicate. Barbiturates depress the emotions, promote a desire to sleep and dull the responses. Aspirin (gr. v-x each 3 hours) may be taken freely to secure rest; rarely it causes urticaria or asthma. Aminopyrine (gr. v-xv) is useful. Pruritus (q.v.) is best controlled by local applications and therapy appropriate to its cause; the itching patient would sleep if he were relieved of his itching. The avoidance of caffeine (coffee, tea and some carbonated beverages) is often sufficient in itself. Benadryl has a useful sedative effect. Chloral hydrate deserves popularity.

Sodium Thiosulfate, commercially photographer's hypo, has been used widely with alleged good effect in metal intoxication, especially arsenic. It is said by some to help contact dermatitis and to be a *general detoxicant; this I do not believe. Extremely* the salt has utility in the prophylaxis of tinea and in the treatment of iodine burns. McBride and Dennie (ADS [illegible]: 63, 19[illegible]) popularized it. Mattice et al. (ADS 4[illegible]: 3[illegible], 1940) did not find that it increases urinary excretion of arsenic, nor did Abramowitz et al. (ADS 4[illegible]: 175, 1943). The Council on Pharmacy (J [illegible]: [illegible], 194[illegible]) omitted it from N.N.R.

Staphylococcus Toxoid is of little aid by itself, and should be used in treatment of the exotoxin. It increases *the antitoxic titer of the blood, yet produces no serious untoward symptoms.* (Anderson and Stokes: ADS 40: 3[illegible], 1939. See also J 104: 542, 1935.)

Streptomycin.—See Antibiotics.

Sulfonamides.—Sulfanilamide, p-aminobenzene-sulfonamide, is a derivative of a red dye. Erysipelas, scarlet fever, chancroid, chronic acrodermatitis, lymphogranuloma venereum, gonococcal infections and other bacterial dermatoses are often strikingly responsive to sulfanilamide therapy (*Strickler and Steiner: ADS 40: [illegible], 1939*). Sulfanilamide is usually tolerated in doses of one to three 0.5 Gm. tablets t.i.d., or in even larger quantities (see Dermatitis medicamentosa). Sulfapyridine [illegible] (p-amino-benzene-sulfonamido-pyridine) is remarkably effective against the same infections as sulfanilamide but causes nausea in small dosage. Sulfathiazole, antistreptococcic and to some extent antistaphylococcic, is another valuable sulfonamide medicine. Sulfadiazine is probably the safest. The utility of these, *welcome as they were a few years ago, has been superseded* to some extent by penicillin and other antibiotics. Dermatologists disapprove the topical application of sulfonamides in any condition. Sulfonamides find their main dermatological usefulness in cellulitis, erysipelas and other streptococcic diseases, lymphopathia venerea, chancroid, dermatitis herpetiformis (sulfapyridine and Diasone), leprosy (Diasone) and, according to some authors, discoid lupus erythematosus.

Sulfur probably exerts little influence except upon *the odor of the stool* when taken internally. It has been given in nail dystrophies. Externally it is a valuable antiparasitic. Its effect on the skin seems to be due to the formation of persulfides in the presence of the sulfhydryl radical present in cysteine and glutathione in the corneum. Petrolatum is better than an emulsion base in promoting the keratoplastic action of sulfur. The keratolytic effect of salicylic acid with sulfur is better than that of either drug alone, the base *being not important. (Strakosch: ADS 4[illegible]: [illegible]16, 1943; 4[illegible]: 3[illegible], 1943.)* A thick paste composed of 30 to 50% sulfur in petrolatum has antiphlogistic, reducing, antipruritic and parasiticidal influences useful in treating seborrheic dermatitis, pityriasis rosea, rosacea, psoriasis, erythrodermas and other diseases, according to Abramowitz (ADS 40: 823, 1939; NYSJM 43: [illegible]46, 1943), who stated that such concentrations are less irritating than weaker ones and seldom provoke sulfur dermatitis. Sulfur is used dermatologically principally in *the treatment of scabies, tinea, acne vulgaris,* seborrheic dermatitis and rosacea. The formula of an attractive vanishing cream preparation containing colloidal sulfur in [illegible] concentration was given by Combes (NYSJM 40: 401, 1940).

Tar.—Crude coal tar, or its alcoholic solution, is a valuable antipruritic valuable in the treatment of atopic dermatitis, lichen chronicus simplex and other disorders. A good prescription is as follows, modified from White:

℞	Crude coal tar	1.0
	Lanolin, sufficient to	mix
	Zinc oxide and cornstarch, of each	10.0
	Liquid petrolatum	10.0
	Petrolatum	to 100.0
Sig.	1% coal tar ointment	

Coal tar will not go into petrolatum directly, but lanolin will take it up, and several proprietary ointment bases will incorporate it nicely. Zetar is miscible in water and makes attractive and satisfactory ointments (Combes: ADS 56: 553, 1947). Downing et al. (ADS 49: 4[illegible]1, 1944) used 5% diglycol stearate in petrolatum as a base for their 6% coal tar ointment, in which 50% cornstarch changed the color from black to gray; the preparation was easily removed from the skin. The tars and their derivatives were reviewed by Obermayer and Becker (ADS 31: [illegible]96, 1935) and by Downing and Bauer (ADS 57: 985, 1948). Their composition is complex, but their empirical usefulness is not to be denied.

Coal tar photosensitizes and perhaps in part for that reason is beneficial in psoria is (q.v.) especially in conjunction with ultraviolet light therapy. Tars derived from the distillation of wood (oleum rusci from birch, oil of cade from j niper) and other tars, such as Ichthyol (a sulfonated bitumen, ichth mmol N.F.) Naftalan and Tumenol (bituminous in origin) were discussed by Sulzberger and Baer (YBD 1931 p. 17), these are not photosensitizers. I think them largely o errated. The selection of the right tar and its right concentration partakes to my notion of th intellectual climate of the medieval ages of dermatologic thought (Sutton: ADS 50: 36 1949)

ICHTHYOL is a bland nd soothing sulfonated bitumen of complex chemistry a tarlike substance of considerable popularity (Stewart et al.: ADS 45: 933, 194). KATT LAN is somewhat similar t Ichthyol in ppearance nd use. These are prescribed in an ointment base in a concentration of 10 t 25% for various manifestations of dermatitis.

Terramycin.—See Antibiotics.

Tetracycline.—See Antibiotics Achromycin.

Thephorin.—See Antihistamine Agents

Thiolutin.—See Antibiotics antifungal.

Thyroid Extract is specific in hypothyroid states and so metimes proves beneficial in acne urticaria, xanthoma, psoriasis and dry scaling derm titides. It administration diminishes lipemia. See Acne treatment

Tyrothrycin.—See Antibiotics.

Vaccine Therapy is often used in furunculosis, carbunculosi infectious eczematoid dermatitis, and dermatitis repens. In acne and sycosis, results a e dubious. Typhoid vaccine is useful as a means of provoking fever artificially (see Heat Therapy) Frei antigen is important in the therapy of lymphogranuloma inguinale. See Foreign Proteins.

Venom.—See Vertebrate Bites.

Vioform, an amorphous powder with the formula 5-chloro- iodo-8-hydroxyquinoline long used as a d sting powder for chronic granulating wounds a d tri homonad vaginitis, possesses in 3% concentration in petrolatum great virtue as an antiseptic in eczematized dermatoses such as exudative intertrigo, sycosis and mixed coccic dermatitis. It was introduced into dermatology by Sulzberger (YBD 1940 p. 16) whose studies of oxyquinoline antiseptics (Sulzberger and Kanof: USNMB 46: 822 1940) were revealing. Diodoquin is one of these (Leifer and Steiner: JID 1.: 703, 1949) but Vioform is the chemical that has become a tried and true friend of the dermatologic practitioner (Reque: Mim. Doctor 25: 203, 1947; Martin-Scott: BMJ 1: 837 1949; Sulzberge and Baer: ADS 58: 224, 1948) Vioform sometimes irritates (Saunders: ADS 54: 456, 1946) and it stains things yellow is not tolerated by persons sensitive to iodine and is incompatible with coincidentally applied mercurial medication; yet it is a significa t dermatologic medicament which I prescribe almost daily. The Ciba vanishing cream preparation utilizes sodium lauryl sulfonate, some stearyl alcohol spermaceti and glycerol. Seldom indeed is this injurious, and it is effective in eliminating staphylococc i from an infected skin. The incorporation of 2% sulfur yields a medicine fairly successf l in scabies, tinea and moniliasis, while the addition of Chloromycetin adds an excellent antistreptococcic and antipyocyaneus effect. Hydrocortisone 1% may be added dvantageously fo eczematous or atopic cases, or omitted, as one wishes. The following formula is one I prescribe with the expectation of removing almost any parasite likely to be present and of soothing a chronic dermatitis:

R	Hydrocortisone	0.2
	Sulfur precipitated	0.4
	Chloromycetin	0.2
	Vioform Cream	20.0
Sig.	HSCV antiseptic cream, for infected eczematous dermatitis.	

The topical application of Chloromycetin in this concentration entails no consequential hazard. The formula is a good one for dermatitis of the hands, otitis externa impetigo, infectious eczematoid dermatitis and bacterially infected tinea. One may use potassium permanganate soaks in conjunction with this, o boric acid poultices may be placed over it.

Vitamin concentrates have proved their efficacy in the relief of conditions due to their inadequate supply or utilization. See Avitaminoses.

MECHANICAL AND PHYSICAL AGENTS

Reference is made to the A.M.A. Handbook of Physical Medicine for accurate and detailed accounts of the use of physical agents. A condensed account of various physical agents used in dermatology including x-rays, radium, ultraviolet, high frequency currents, galvanic currents, and solid carbo dioxide, was given by Cipollaro (J 137: 134, 1948)

Instruments the dermatologist likes to have immediately at hand include suitable magnifiers, a microscope a scalpel with disposable pointed and round bellied blades forceps, needle holder and hemostats for minor dermatologic surgery a set of cutaneous punches probe curet, comedo extractor (I use magnifying spectacles, pointed scalpel and fingernails) sphygmomanometer stethoscope ophthalmoscope and otoscope reflex ham-

mer vibrator fork flashlight Wood's light hair clipper electric shaver needles and syringes sterilizer interval timer and special equipment as described hereinafter. Supplied with these things, a license to practice and a bookkeeper a young fellow could hang out his shingle but he must not overlook medical liability insurance.

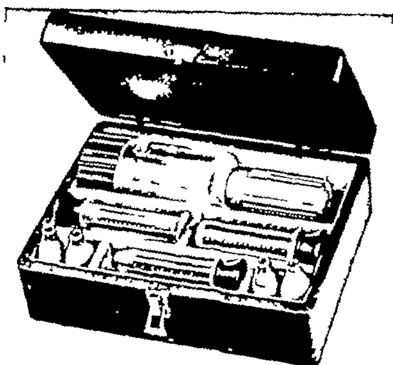


Fig. 41. Solid carbon [illegible] [illegible] [illegible] [illegible] [illegible] with [illegible] of this kind. (Kidde Manufacturing Co., Inc., Bloomfield, N. J.)



Fig. 42. [illegible] solid carbon dioxide firmly for [illegible] or [illegible] seconds to small [illegible] human [illegible] [illegible] results [illegible] cure with almost undetectable [illegible]

Refrigeration (Cryotherapy).—Pusey in 1907 introduced the use of solidified carbon dioxide nowadays obtainable as dry ice. A bit of this refrigerant whittled to appropriate shape and held in cotton to protect the fingers, is applied to the lesion for a period of from [illegible] seconds to a minute. The degree of freezing depends on the duration and pressure of application. A slush of solid carbon dioxide and acetone is also valuable. The agent causes erythema peeling blistering or deeper destruction and so is useful when these purposes are desired see Hemangioma, and Acne treatment (Alderson

ADS 37 234 1937; Carpenter: J 118 290, 1942) Liquid oxygen was thought easy to use and valuable by Kile and Welsh (ADS 57 57 1948) although I have been disappointed with it and with liquid nitrogen too

Actinotherapy.—Light irritates the skin and produces inflammation. It acts directly on the epithelium and the most superficial blood vessels. It induces sweating exerts an antiparasitic power and in overdoses may produce serious disturbance (see Sunburn) Its effect largely depends on the character of its constituent rays. If these are from the lower end of the spectrum yellow or red of long wave length, the skin is little affected but short wave lengths, the violet and ultraviolet may produce tissue destruction. (Cipollaro APhysTh 21 223 1940; Krusen APhysTh 22 199 1941 Council Report J 121 26 1943) Ultraviolet treatment has special value in tuberculosis of the skin (q v) and peeling doses cure pityriasis rosea and alleviate acne temporarily Combined with tar ointment it is a standard treatment of psoriasis (q v) but otherwise its indications in dermatology are few (Cleveland CanadMAJ 37 558 1937)

Locally satisfactory results are obtained from the use of 500 to 1 000 watt incandescent lamps in impetigo contagiosa and similar disorders. The effects are probably due to radiant heat and to the fact that drying abets the self-sterilizing of the skin.

Roentgen Therapy.—X rays produce degenerative changes in all tissues. Their effect is apparently proportional to the mitotic activity of the cellular structures.

The Primary Biologic Effect of Irradiation is one of cell injury When the degree of injury is small, the tissue eventually may be able to recover from it. Hence in general it is undesirable to irradiate normal tissue and one tries to irradiate not more of the normal tissue than necessary while treating a lesion.

Precautions must be taken to protect personnel working with radioactive materials from receiving enough radiation to damage them 0 1 r per day is the maximum allowable

Protection of the operator who should take every precaution to prevent irradiation of himself was described by Taylor (J 116 136 1941) Protection and radiation hygiene were fully discussed by Quimby and Pool (Radiol 41 272, 1943) see also Council on Physical Medicine (J 183 818 1948)

Biologic Action of X-rays depends on energy which is absorbed not on that which passes through The influence of wave length is negligible The effect on tissue is analyzable in terms of effect on cells. The action is necrobiotic although with small dosage the injury may be subliminal After a brief latent period, shorter with heavy dosage living cells treated with x rays manifest progressive turbidity and granular alteration of the cytoplasm, lose their motility and cease mitotic activity After a period of inactivity they may resume a normal function or they may suddenly die or their granular dissolution may occur promptly if dosage is heavy Histologically one finds cytolysis pyknotic degeneration, fragmentation and vacuolation. Cell types may be listed according to their radiosensitivity in order of greater to less lymphocytes, mucous cells of salivary gland and intestine spermatogonia epithelial endothelial young connective tissue cartilage muscle bone fat and nerve cells. Bacteria are insensitive, and, in general *doses which would kill parasites would be much more than sufficient to necrotize the tissues of the host*

Response of living cells to lethal amounts of x ray energy were studied by ultraviolet light microscopy by Montgomery and Warren (Sci 117: 589 1953) Profound changes became conspicuous 48 hours after the dose with loss of UV absorption by both the cytoplasm and nucleus, and nuclear swelling When ionizing particles were applied to particular small portions of cells as a microbeam a few dozen protons applied to chromosomes were found to produce severe aberrations but much more were required to be applied to cytoplasm to produce any effect reported Zirkle and Bloom (Sci 117 487

1953) Radiobiologic mechanisms were considered by Kulwin and Buley (ADS 70 417 1954) who discussed the physicochemical effect of the ionizing particle as it produces a track of ionization sheathed with a layer of hydrogen and hydroxyl ions capable of altering enzyme systems. The lack of oxygen increases protection against the damaging effects of x rays in many biologic systems (Latt Physiol Rev 33 35 1953) *Epilation following x ray treatment did not occur in small areas where the circulation of the blood was occluded by pressure* observed Schwarz (MünchMWchn 24 1217 1909) It required 2 or 3 times as much soft radiation to epilate in mice skin areas rendered anoxic by mechanical clamping as was required in controls in experiments of Strauss et al (JID 22 129 1954) but anoxia did not influence the size of the dose necessary to produce permanent alopecia

If one knows how cells react to x rays and of what kinds of cells the skin is constituted then one can picture the skin with permanent x ray damage it is a skeleton of anuclear fibrotic tissue in which epidermal accessory structures are lacking capillaries few fixed tissue cells wanting and epithelium sickly and thin See X ray and Radium Injuries.

The action on pathologic lesions of radium rays like x rays depends on the *sensitiveness of the particular varieties of cells affected* This applies to benign inflammatory and malignant processes. The leukocytes are the most sensitive of all human cells. Young connective tissue cells are comparatively sensitive and mature connective tissue cells are comparatively insensitive to irradiation. The most sensitive ocular structures are the conjunctiva and epithelium of the crystalline lens. Doses of radiation insufficient to cause an inflammatory reaction of the eyelids are not likely to cause the conjunctiva or lens to react *Doses sufficient to produce conjunctivitis may lead to the* formation of cataract months or years later especially in children See Warren (J 133 462 1947)

The testicles are not so sensitive as may be supposed and scrotal lesions may be treated with less concern than might be imagined according to Calloway et al (ADS 56 471 1947) who found that it required 900 r on the scrotum of the rabbit to cause sterilization

The abdomen of the pregnant woman must not be irradiated yet I have not seen an article on the facts pertinent to this proscription

Sequelae of dermatologic therapy were studied by Sulzberger et al. (ADS 65 639 1952) who presented conclusive evidence that total doses reaching 1000 r given for acne dermatitis and psoriasis resulted in no after-effects, and doses up to 1400 r did not produce cancer ulceration or dangerous sequelae

X RAY DOSAGE is cumulative If a particular area of skin receives therapy repeatedly the case record must show not only the dose given at any one treatment but also the total dose Meticulous records must be maintained Such records are a great comfort if a case goes to court for alleged malpractice If one uses x ray therapy one must expect sooner or later to be sued The defense must be watertight

Using the usual dermatologic machines and usual dermatologic doses of from 75 to 150 roentgen units (150 r is a rather large dose from the dermatologic standpoint) at 100 KVP a practitioner hesitates to exceed 1500 r total unless he is treating neoplasia The curative dose for skin cancer (q v) *is in the vicinity of 3000 r total and one expects this dose to result in* permanent atrophy One is willing to induce permanent changes with x rays, as with knife or electrocautery when ablation of tissue is the purpose of treatment Yet a surgical scar is in general to be preferred to a radiation scar for the latter may result in chronic ulceration requiring excision or in the evolution of keratoses or x ray carcinoma (q v)

Prior to adding more x ray therapy to an area previously irradiated one must know how much x ray therapy that site has received in the past. Inquiry is made of the patient, and letters are addressed to his previous doctors. X ray damage results from unwise prescription or erroneous delivery of the

planned dose such as omitting the filter when calculation was made for the use of filtered radiation X ray damage is avoidable Most x ray injuries I see these days have resulted from the patient s own carelessness the dentist held films in his patients mouths because he was in too great a hurry to teach the patient to hold them for himself or the surgeon was careless in fluoroscopy X ray as a tool has long enough been known and its potentialities for harm are sufficiently familiar by now so that burns resulting from stupidity are rather infrequent Whoever intends to use the agency must indeed possess wisdom and exercise respect for its capabilities.

Dosage — For the rough estimation of the dosage of unfiltered radiation Andrews used the formula

$$\frac{\text{current} \times \text{peak voltage squared} \times \text{time}}{\text{distance squared}}$$

and, substituting experimentally determined numerical values, he stated that with a particular apparatus, an exposure involving 2 milliamperes, 100 kilovolts (a spark gap between points of about 6 inches) and 3 minutes exposure at a distance of 8 inches produces mild erythema

Doubling the milliamperage doubles the dose.
Doubling the duration of exposure doubles the dose.
Doubling the voltage quadruples the dose.
Doubling the distance quarters the dose.

Materials placed between the anode and the recipient skin act as filters and obstruct the long (soft) rays much more than the penetrant short (hard) rays. Opacity depends on the atomic weight of the material of which the filter is composed. Tissues themselves filter the beam Since the first millimeter penetrated cuts out a certain percentage of the incident rays of a given wave length and the next millimeter cuts out the same percentage of the rays that reach it, the effect of thickness of filter is to obstruct the energy in the manner of compound interest Interposition of filters enables a dose to be given which is comparatively uniform in wave length so that only the hardest rays reach the skin, and the beam, being relatively homogeneous, is absorbed at a single percentage rate per unit of tissue depth. The *roentgen unit* is that quantity of x radiation which liberates one electrostatic unit of electricity when passing through 1 cc. of air at standard temperature and pressure This is the International Standard of x ray dosage, and the dose is measured in these units by means of an iontoquantimeter which in simplest terms, is a chamber, the contents of which ionized by the beam of radiation, are attached to a charged electroscope the rate of discharge of which measures the ionization and so measures the quantity of x rays.

The half value layer HVL, is that thickness of a filter which obstructs half the energy of the incident beam. HVL increases as the wave length diminishes, that is, as the hardness of the beam increases. About twice the thickness of skin will obstruct the same proportion of radiant energy as a unit thickness of aluminum The effect of soft rays per absorbed r rises in direct proportion to the HVL, and the differences in skin reaction to equal surface doses are due to differences in depth dosage (Ebbehj ActaD-V 32 117 1952) The quality of x rays selected for treatment of a given case should have HVL approximately equal to the thickness of the diseased tissue Grenz rays with HVL of from 0 1 to 0 4 mm of skin are suitable only for superficial dermatoses but for these they may be especially suitable

The threshold erythema dose is considered an important biologic measurement by Belisario (ADS 46 619 641 194.) who standard ed the use of a 1.0 cm. circular area on the proximal a t rior thigh for is measurement so that accurate comparison of results could be tested by various observers. Belisario stressed the tissue injury factor and the effect of oxygen tension. The usual practice in dermatologic therapy is to measure dosage by units a delivered in ai t the surface f the treated area, but this is crude measurement, as is known by both the ph cist and the b ologist. Its determination depends on that quantity of irradiation from a particular machine whi h produces faint but defi x te redness in a normal skin. Th erythema dose at 100 KV peak u filtered is about

300 r (MacKee and Cipollaro: ADS 41: 1 1940). The E dose increases with increased hardness of the ra[illegible] but remai[illegible] the best sta[illegible]d[illegible]rd test of dosage in th[illegible] opinion of Belisario (ADS 45 [illegible] 194[illegible]). Variabl[illegible] and complexities entering int[illegible] the ph[illegible]icist's estimation of [illegible] make the erythema dose (E) a[illegible] most logical[illegible] pra[illegible]tical one (Belisario: Brit J Radiol 23 [illegible] 195[illegible]).

DOSAGE CONSIDERATIONS.—Details of x ray theory and therapeutic technic require more extensive exposition than may be given here. Knowledge of the teachings of MacKee and Cipollaro (X Rays and Radium in the Treatment of Diseases of the Skin, Lea & Febiger, 1946) and adequate supervised instruction in the use of roentgenologic apparatus are essential.

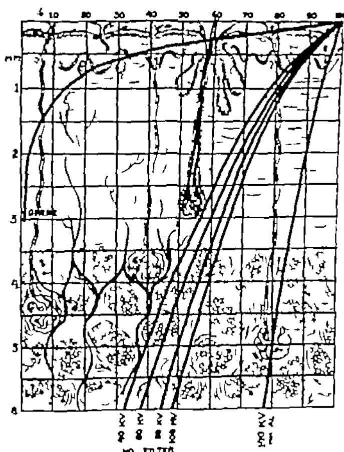


Fig. 76.—Roentgen radi[illegible]tion [illegible]bsorption curves, indicating depth dosage [illegible] modified by [illegible]oltage [illegible] filtration. (Cipollaro and Mutscheller: ADS 41: [illegible] 1940.)

Substances including tissues, which are irradiated become themselves sources of secondary irradiation during their irradiation. Secondary irradiation and backscatter provide a consequential proportion of the dose actually received within the tissues. On this account the size of the portal through which the rays reach the skin is significant. A larger dose as measured at the skin surface is necessary to deliver an equivalent dose within the tissues when the portal is smaller. At 120 KV without filtration added to that which is inherent in the tube the erythema dose as it varied with the portal was estimated by Goldberg (ADS 49: 346 1944) as follows:

Diameter	E dose	r units
10 mm	1.5	810
8	[illegible].5	850
6	3.5	1[illegible]00
4	5.0	1[illegible]00
[illegible]	8.0	2[illegible]00

The skin dose received exceeds the air dose measured at the skin surface significantly because of the exit dose which is that part of the incident energy which passes through The air dose does not adequately express the amount of radiation received by the skin Applied to the hand as pointed out by Andrews et al. (ADS 50 355 1944) at 65 KV skin dose exceeds air dose by 25% at 100 KV by 45% and at 135 KV with 3 mm Al filtration by 78% See Shafer et al (ADS 59 472 1949) on exit and backscatter factors in dermatologic therapy

Other considerations of dosage are elaborated by MacKee et al (ADS 47 490 657 1943) A time factor is concerned for a certain quantity of radiation must be administered before any cells are destroyed and cells recover from irradiation so that low intensity of radiation decreases its effectiveness. An area factor is concerned for the erythema is smaller than the mask which determines the portal by about 1.5 mm for unfiltered radiation and 3.0 mm for filtered. Therapy apparatus, furthermore does not deliver a beam which is uniform in intensity laterally from the central ray so that overlapping of fields cannot be done correctly unless the outer rays of the beam as well as the central rays have been calibrated.

SHIELDING —In administering a dose of x ray therapy to that part of the skin which one intends to treat it is essential that all the rest of the skin be shielded A metal cone attached to the tube delimits the beam effectively but the beam from the cone is further delimited, standardly with lead impregnated rubber laid on the patient in such a way as to control accurately the field to be exposed. Further control of the field is exercised by means of a sheet of 2 pound lead (of a thickness such that a square foot weighs 2 pounds) and the hole through the lead may be made any convenient and appropriate shape A Craftsman electric drill is an excellent tool for shaping small irregular holes, such as are required in treating verrucae keloids, hemangiomas and carcinomas. Another solution of the problem of shielding small, irregular fields was perfected by Wilson and Luikart (ADS 64 580 1951) utilizing a bismuth putty easy to prepare and easy to carve This putty was about 60% as effective as an equal thickness of lead. Lead foil 0 03 inch (0 76 mm) thick lets no energy through at 100 KVP (Landauer and Landauer ADS 61 864 1950)

RADIATION IN TREATMENT OF DERMATOSES.—In the following diseases roentgen therapy is especially useful

Acne	Granuloma pyogenicum	Lichen planus
Actinomycosis	Hemangioma	Lymphoblastoma
Blastomycosis	Hyperidrosis	Psoriasis
Bromidrosis	Inflammations	Sarcoma
Carcinoma	Keloid	Sycosis
Favus of scalp	Keratosis	Tinea capitis
Folliculitis keloidalis	Lichen chronicus simplex	Verrucae

X ray therapy is conspicuously contraindicated in lupus erythematosus. It does no good in pemphigus, dermatitis herpetiformis, diseases caused by animal parasites, or diseases due to primary physical or chemical injury Few bacterial diseases are benefited, other than furuncle carbuncle and erysipelas. When exudative dermatitis becomes worse immediately after x ray therapy there is likely to be a pathogenic micrococcus present Chronic dermatitis of the hands is a condition in which temporary benefits from repeated doses of x ray therapy are likely to be followed by eventual cumulative overdosage.

Seldom does a dermatologic patient receive so much x ray as to injure his hematopoietic system. Yet in the treatment of widespread dermatitis, this possibility must be borne in mind The standard 375 r 5-point epilation for tinea capitis does no harm, but the child may vomit 12 hours after receiving the treatment.

Radiation in Treatment of Inflammation —A furuncle consists of living staphylococci in the central region surrounded by fibrin and by living and dead leukocytes some of which have engorged some of the cocci This lesion is set within the dermis which consists in the main of collagenous and elastic fibers, fibrous cells, blood vessels and lymph vessels. The damage by bacterial activity is greatest at the center less peripherally it suffices to evoke vasodilation (redness) in the outer zone intracellular swelling and intercellular exudation of proteinous fluid as well as redness in the mid zone and necrosis at the center When x rays are applied the leukocytes dissolve the capillary endothelium swells blood flow is obstructed so that redness disappears, *the exudate is resorbed and no one knows what happens to the bacteria* Sometimes the lesion shows exacerbation for a few hours, but the customary clinical effect of roentgen treatment of a furuncle is to cause its prompt disappearance the effect is similar upon a carbuncle (usually) and is analogous in any other inflammatory disease Perhaps antitoxic substances are liberated (Bisgard et al Radiol 39 691 1942) Cellulitis is favorably influenced (DeHollander AmJR 48 811 1941) See Shaffer (JID 3 159 1940) Sutherland (AmJMSc 198 729 1939) Desjardins (J 116 225 1941 Radiol 38 274 1942); Edit (J 131 1424 1946)

Local sensitivity is abolished temporarily by x rays seemingly by their effecting the disruption of the cells on which local reactivity depends. The manifestations of contact dermatitis or fungous infection may be made to disappear but respectively the allergen is not removed or the fungus itself remains When *the skin regains its ability to react it does so. The clinical* cycle is disease treatment cure recurrence treatment cure —and eventually there results irremediable x ray damage The same old infection is still superimposed the more difficult to get rid of and medicolegal complexities arise

Radiation in Treatment of Neoplasms.—There are analogies between the application of radiation and the application of a caustic paste In either case cure if cure results, depends on destruction. In either case one does not know what the exact boundary of the destruction is going to be and in either case one does not command this boundary but simply intends that it will be sufficient Except in palliation and under uncommon combinations of circumstances I prefer surgical attack if it is feasible where with a single procedure one takes definitive steps to destroy that tissue which in one's judgment ought to be destroyed and leaves healthy that which one does not wish damaged. The surgical scar is not an x ray burn

Grenz (Infraroentgen) Radiation designates therapeutic electromagnetic vibrations ranging in the spectrum between the usual roentgen rays and the ultraviolet rays. No wave lengths are used longer than 1.7 angstrom units (spark gap equivalent of about ¼ inch between points of sewing needles) They are capable however even in therapeutic doses, of producing superficial atrophy and telangiectases. Absorption is almost complete in the external 3 mm. of the skin, so that while telangiectases may indeed occur sequels are rarely serious (Hollander JID 1: 15 1938)

The use of soft x rays, produced by a Chaoul tube close to the lesion under treatment, simulates the effect of radium, energy from which falls off rapidly as distance increases. *The equipment consists, essentially of a shock proof tube the rays emerging through* the 0.2 mm nickel target, which serves as anode window and filter alone. By daily treatment a huge total dosage may be built up according to the Coutard plan, and the radiation, originating actually in contact with the tissues that receive it produces locally typical roentgen destruction.

Low voltage therapy requires knowledge of how to diminish errors of dosage due to the lack of good voltage-regulating machinery according to *Pillsbury et al. (ADS 70 16, 1954)* who called attention to difficulties of dosage measurement and structural defects of some therapy units. Doses of at least 150 r are needed, *for* smaller doses accomplish nothing Erythema is produced by 500 r is more intense at 1000 r is sharp and accompanied by swelling at 1500 r A single dose of 3700 r produced atrophy Cumulative doses of from 4000 to 6000 r were followed for several years and no sequelae of consequence were seen. Early erythema fades into pigmentation usually within 7 days, and pigmentation may persist for several months (Domonkos JID 22 369 1954)

REFERENCES ON GRENZ THERAPY

Andrews: ADS 58: 118, 1948 (Philips contact equipment stray radiations, hazards to operator value in small superficial epitheliomas, hemangiomas, keratoses, warts)
Bloch: AJRoentgenol. 3 480 1944 (grenz ray use)
Bl...: DMW 75 318, 1937 (contact therapy)
Bucky and Combes (Grenz Ray Therapy, Springer Publishing Co., 1954) history development and use of apparatus, effect and evaluation.
Cipollaro: ADS 421 14 1940 (beryllium window)
Goin: Radiol 42, 248, 1944 (Philips Metalix type tube, HVL 0.2 mm. Al, 50 KV 2 ma)
Harding: ADS 58 390, 1948 (rays with HVL 0.025 mm. Al)
Hollander and Shelton: ADS 37 279 1938 (Chaoul therapy)
Howes and Camiel: AmJR 48 340 1942 (contact therapy)
Jungma n: IDJ 61: 181 1939 (grenz ray therapy of lupus, chronic eczema, Darier's disease)
Leitner: DJPhy M 6: 114, 1943 (grenz rays at 8 to 12 KV; little energy reaches cutis)
Pendergrass et al.: Radiol 32: 142, 1939 (Chaoul tube dosimetry)
Ryan: IDJ 64: 47 1942 (grenz ray in acne, herpes, granuloma annulare, neurodermatitis)
Winkeyer: BMJ 1 948, 1954 (uses of x-ray therapy for dermatoses and inflammations)
White: APhysTh 18 139 1937 (grenz ray therapy)

Radium possesses one great advantage over x rays in that it can be placed in the throat and similar cavities and brought into contact with diseased tissues difficult of access. The story of the discovery of radium and of Mme Curie's gram of the substance was interestingly told by Voll (Rad 17 37 1921). Radium taken internally enters osseous tissue permanently especially the mandible where its radioactivity eventuates in sarcoma. See Evans (AmJPubH 23 1017 1933 AmJR 37 368 1937 AnnIntM 11 1443 1938)

Radium as such does not have any therapeutic value. The tissue reactions which follow radium treatment are the result of the absorption of energy by the tissue from the radiations emitted by radium and its disintegration products, stated Desjardins and Williams (J 130 207 1946) whose article is extensively quoted hereinafter. An exposition valuable to the non physicist and accurate, is that of Hecht and Rabinowitch (Explaining the Atom Viking Press 1954) considerably more up to date with respect to atomic energy than this essay of Desjardins and Williams, which I nevertheless continue to quote

"Radium is a member of 1 of the 3 radioactive series which occur in nature. The atoms of a radioactive element eventually change into atoms of another element, and this change, or disintegration, is produced by the original atom losing mass and energy. The lost mass and energy are in one or more of three forms of radiations, called the alpha rays, beta rays, and gamma rays.

"Alpha rays are nuclei of helium atoms which travel at a velocity which may be as high as a tenth of the velocity of light. The emission of an alpha ray by an atom a loses its atomic weight 4 units and its atomic number (number of units of positive charge in the nucleus) 2 units. Although the energy of an alpha ray is quite large, it cannot travel far through solid materials; the greatest distance it can penetrate tissue is about 0.1 mm. and through materials of greater density the distance would be even less. The wall of all the ordinary containers used to hold radium or other radioactive materials is thick enough to stop all the alpha rays.

"Beta rays are electrons which travel at a velocity which may be as high as 99 per cent of the velocity of light. An electron has a mass of approximately one two-thousandth of an atomic unit of mass and has 1 unit of negative electric charge; hence the emission of a beta ray by an atom does not produce any significant change in its atomic weight, but it increases its atomic number 1 unit. The average energy of a beta ray is of the order of a tenth of the energy of alpha rays. Because of their greater velocity, smaller mass and smaller electric charge, beta rays are much more penetrating than alpha rays. Beta rays can travel through tissue a distance of approximately 10 mm. A thickness of metal sufficient to stop all beta rays is often called a beta-ray filter and for the commonly used metal these thicknesses are 0.5 mm. of Pt or Au, 1 mm of Ag or Pb, or 2 mm of brass, monel metal, or steel

"Gamma rays are electromagnetic radiations of shorter wave length than most roentgen rays, ultraviolet light, visible radiations, and radio waves. Like all electromagnetic radiations, they travel at the same velocity as light. The emission of a gamma ray has no effect on the atomic weight or atomic number of an atom. Gamma rays are generally emitted by the same atoms that emit beta rays. In general, the energy of the gamma rays is a little greater than that of beta rays, and they are much more penetrating than either the alpha or beta radiations. One centimeter of tissue reduces the intensity of the gamma rays about 5 per cent. A half inch of lead reduces their intensity about 50 per cent, and some of these rays can be detected through 6 inches or more of lead.

"It is not possible to predict when any particular atom of a radioactive element is going to disintegrate, but a definite percentage of the atoms present at the beginning of a period of time will disintegrate during that period. For each radioactive element the rate of disintegration is different and characteristic. Hence the period of time which elapses before half of the atoms disintegrate is called the 'half life period'; this also is characteristic of each radioactive element. The rate of disintegration of an element is not affected by chemical combination, extremes of heat, cold, pressure or vacuum, or by anything which can be done to the element" [except by procedures inducing atomic fission]

ELEMENT	ATOMIC NUMBER	ATOMIC WEIGHT	PHYSICAL STATE	RADIATION	HALF LIFE PERIOD
Radium	88	226	Solid	Alpha	1,590 years
Radon	86	222	Gas	Alpha	3.82 days
Radium A	84	218	Solid	Alpha	3.05 minutes
Radium B	82	214	Solid	Beta and gamma	26.8 minutes
Radium C	83	214	Solid	Beta and gamma	19.7 minutes

If a preparation of pure radium (radium being used as a specific example although any radioactive element could be used as well) is sealed in a tube, the tube immediately contains other elements. The amount of these elements will increase for a time and the amount of radium present will gradually decrease. However, since radium disintegrates slowly, *the amount present will remain essentially constant for many years,* and hence the number of atoms of radium disintegrating in any period of time—which is the same thing, the number of atoms of radon formed in any period of time—will remain essentially constant for many years. The amount of radon present gradually increases until the number of atoms disintegrating in a period of time is just equal to the number of atoms being formed (number of atoms of radium disintegrating) in the same period. From then on, the amount of radon present decreases as the amount of radium present decreases; the ratio of the amounts of all those present is always the same and radon is then said to be in equilibrium with radium. In a similar manner equilibrium eventually will be established between all succeeding members of the radioactive series. Between radium and radium C, equilibrium is established in about 2 months, but it takes only about 4 hours for equilibrium to be established between radon and radium C. The amount of radon in equilibrium with 1 Gm. of radium is called a curie and smaller amounts are measured in millicuries or microcuries.

Radium is commercially available only in the form of a salt, generally the sulfate, bromide or chloride, and generally a small percentage of the total weight of the preparation is the corresponding barium salt. However, the preparation is described as containing a certain weight of radium, which is the actual weight of the radium element present and not the total weight of the preparation. The actual amount of radium present is determined by comparing the amount of gamma radiation emitted by the preparation (after equilibrium has been established with radium C) with the gamma radiation emitted by a preparation whose radium content is known, or by measuring the rate at which radon is formed. Similarly the amount of radon contained in a tube is generally measured, after equilibrium has been established with radium C, by comparing the gamma ray emission with that from a tube of radium, since the intensity of the gamma radiation from 1 mc. of radon is the same as the intensity of the gamma radiation from 1 mg. of radium, when the two are in equilibrium with radium C. Most commonly the intensity of the gamma radiation is measured with an electroscope or other suitable instrument by determining the amount of ionization produced in a given volume of air.

"Since in ordinary radium treatment only the beta and gamma radiations are used, radium B and radium C are the only elements actually needed because they are the source of these radiations. However, they disintegrate rapidly and radium or radon is needed as a constant source for supplying radium B. An applicator containing radium will maintain nearly a constant amount of radium B and radium C for many years, while an applicator containing radon decreases in strength approximately a sixth every twenty four hours, or a half every 3.82 days, and does not have any therapeutic value after about a month because all the radon and radium B and radium C have disintegrated. Since radon is the only gas in the disintegration series, it can be separated rather easily from the rest of the series, and applicators containing radon are frequently used instead of applicators containing radium: so-called 'radium therapy' may be given with either type of applicator.

Treatment with radium can do more harm than good. To determine the best method of applying radium and the most suitable dose in each case requires training and judgment and the best results are obtained only by physicians who have had extended experience. For these reasons responsibility for treatment of this kind should be limited to qualified specialists.

"Ordinary radium therapy can conveniently be divided into three general types of application.

"In **External Irradiation** the radium applicator is either in contact with the skin or at some distance from the skin. Plaques containing radium, radon bulbs, tubes of radium or radon, and radium bombs are the common types of applicators used for external irradiation. [See Morrow and T[illegible]: [illegible] 33 [illegible], 193[illegible].]

PLAQUE APPLICATORS usually contain from 5 to 25 mg. of radium embedded in the surface of a glazed material having an area of from 1 to 8 square centimeters. The filter in plaques is very small, seldom more than 0.1 mm. of monel metal; hence most of the beta rays may be used. Plaques are generally placed in contact with the lesion to be treated and are used for surface lesions when irradiation is to be confined to a shallow depth. Although gamma rays also are emitted, their effect on deeper tissue will be slight during the time the beta rays produce a much greater effect on the superficial tissue.

RADON BULBS are thin-walled bulbs of glass, generally less than a centimeter in diameter, containing radon. Since the filtration of the glass wall is very slight, most of the beta rays may be used. Sometimes these bulbs are used instead of radium plaques.

"TUBES containing radium or radon generally have walls thick enough to absorb all the beta rays, *so that only gamma rays may be used.* Walls *thicker than a 'beta ray filter'* make a mechanically stronger tube but reduce the intensity of the radiation. The 'active length' (length of radioactive material) is generally about 1 to 2 cm.; the over-all length of the tubes from 1.5 to 3 cm., the outside diameter from 3 to 7 mm., and the wall thickness 0.5 to 2 mm. platinum equivalent (platinum or sufficient thickness of other materials to give a filtering effect equivalent to that of platinum). Often a few millimeters of rubber, bakelite, wood or similar organic filter is used between the tube and the tissue to absorb the secondary radiation from the tubes. Tubes generally contain from 5 to 100 mg. of radium, or up to several hundred millicuries of radon. Tubes are sometimes placed in contact with the skin, but more commonly they are separated a few centimeters from the skin.

RADIUM BOMBS usually contain from 1 to 10 Gm. of radium, which is enclosed in a large block of lead (or other dense metal) with an opening through which radiation can emerge. *Filtration is approximately the same as for tubes,* but the distance between the radium and the skin usually varies from about 10 to 40 cm.

"In **Intracavitary Irradiation** the applicators are placed in a natural cavity of the body, usually in order to bring the applicator closer to the lesion to be treated. The most common applicators used are the same radium and radon tubes which are used for external application. The tubes are often enclosed in rubber or similar material to absorb some of the secondary radiation from the tubes and to increase the distance between the tube and the tissue.

"In **Interstitial Irradiation** the applicators are inserted into the tissue to be treated. Radium or radon needles, containing from 1 to 10 mg. of radium or mc. of radon, with filtration of from 0.3 to 0.5 mm. of gold or platinum are often used. After the desired dose has been given, the needles are removed. Small tubes containing radon are often used, but these are never removed; they contain such an amount of radon, *usually from 0.25 to 2.5 mc.,* that the desired dose will be delivered while all the radon disintegrates. These are commonly called permanent implants, radon seeds, gold implants or gold seeds and generally are made of pure gold having a filter of 0.3 to 0.5 mm., an outside diameter of from 0.75 to 1.15 and a length of from 3 to 6 mm. They also may be made of platinum.

"During recent years, in dealing with resistant tumors, the tendency has been to eliminate most or all of the beta rays by using as a filter 0.5 mm. of platinum or an equivalent thickness of some other metal. The reason for this is that beta rays have a decidedly caustic or necrotic effect at short range, that is, on the tissues immediately adjacent to the radioactive

substance. This is commonly accompanied by severe pain. Elimination of beta rays by increasing the filtration prevents this necrotic effect and concomitant pain. Lead as a filter is generally employed only to treat superficial lesions.

"The dose of radiation delivered to the tissue—the amount of energy absorbed by the tissue from the radiation—depends on the amount of radium or radon used, the length of time of application, the arrangement of the applicators, the filtration and the distance between the source and the tissue. The biologic effect produced by irradiation depends on the dose and many other physical and biologic factors, including the rate of which the energy is absorbed, the volume of tissue irradiated and the dosage distribution throughout that volume, the kind of tissue, the phase of the life cycle of the cells, the blood supply and many other factors.

[Interstitial radium therapy technic was lucidly described by Lehman and Pipkin (ADS 631: 312, 1951; J 154: 4 1954).]

"Dose is generally expressed in milligram-hours or millicurie-hours, the former being used for radium salts, the latter for radon; the two terms describe practically the same quantity. In ordinary use, however there will be a slight discrepancy in their values if the change in value of the radon during the time of treatment is not taken into account. If the average value of radon is used, this discrepancy is practically eliminated for any normal period of treatment. To describe a treatment completely the amount of radium or radon, the time of application, the filtration, the distance from the lesion, and the type of applicator should be given. The roentgen (r) is a measure of the amount of energy absorbed from the radiation hence it takes into account the amount of radium or radon, time, arrangement, distance and filter. The dosage rate at a distance of 1 cm. from a point source of 1 mg. of radium filtered by 0.5 mm. of platinum, is approximately 8.4 roentgens each hour. When the entire dose is given within a few hours, about 1 000 roentgens of gamma radiation is required to produce an erythema of the skin. Among advanced workers there is an increasing tendency to express radium dosage in roentgens, but at the present time methods of measurement have not yet been perfected and simplified sufficiently to make this a general rule.

"The Maximal Safe Dose of radiation which a person may receive day after day called the 'tolerance dose' is generally considered to be about 0.1 roentgen each day. The dose received by persons working with radioactive materials should be measured by having them carry on their person photographic film or suitable dosage measuring instruments. When the dose which they receive is near or more than the tolerance dose added protection should be provided. It is advisable also to have frequent studies made of the blood of the personnel, for some of the earliest tissue changes produced by irradiation are indicated by changes in the blood."

Radium Dosage and Effects.—Gamma rays of radium are identical, except for their shorter wave length, with x rays. They have like properties but are highly penetrating. In the use of radium intensity is greatest at the surface of the applicator which is the source and the analogue of the tungsten target within the x ray tube. Intensity falls rapidly as distance increases from the radium applicator whereas x ray intensity within the depths of practical concern is comparatively uniform. Thus radium burns are in general smaller in all three dimensions than x ray burns.

The dose with radium or radon is estimated in milligram hours (or millicurie hours) per square centimeter at a given distance with filtration described, or milligram hours (millicurie hours) per cubic centimeter of tissue when needles or seed are implanted. Cole and Driver (AmJR 33: 69–, 1935) described their interstitial use of platinum needles of 27, 44 and 60 mm. length carrying 1, 2 or 3 tubules of radium each 15 mm. long. The over-all diameter of the needles was 1.65 mm., the wall being 0.5 mm., sufficient to filter out all the alpha and most of the beta rays. Such needles will destroy they found, 1 cc. of squamous-cell carcinoma in days. If placed 1 cm. apart each cubic centimeter of tissue receives 116 mg hr of gamma irradiation. They found that failure resulted more often from failure to recognize the dimensions of the tumor than from other reasons. Dangers in the use of radium and radon were elaborated upon by Cipollaro (J 116: 1906, 1940) whose conservatism is to be approved.

Gamma Ray Treatment using radium distributed on external applicators and molds was systematized so as to deliver correct dosage in a practical manner by Paterson and Parker (BJRad 7: 59?–632, 1934); see Squamous Carcinoma, treatment also Meredith et al (Radium Dosage The Manchester System, Livingstone 1947). See p. 1290

The Action of Radium Rays on a tumor depends on the kind of cells of which the tumor is chiefly composed. Each variety of cells in the body has a specific range of sensitiveness to the rays, and the sensitiveness of neoplasms corresponds closely to that of the normal cells from which the tumor derived. The sensitiveness of cells appears to depend chiefly on their life cycle mitotic activity. Radium rays appear to act mainly on the genetic elements of the cells and thus may cause cellular activity to be inhibited or be completely arrested and the cells to be injured or to disintegrate completely. The rate of this effect varies with each variety of cell and with the age of the cells.

Radon (Emanation).—There exist 3 series of radioactive elements, the uranium, actinium, and thorium series. Each member of a series is a chemical element. Each differs from the next in its series by either an alpha particle (helium nucleus) or a beta particle (electron). Emanation develops at known rates from each member of the series, and can be separated, sealed in tubes, and used separately. The half value period of radon is 3.8 days. A millicurie (mc.) is an amount of radon which will produce the same gamma ray effect as 1 mg. of radium. A gram of radium will produce 184 mc. of radon per day. Tubes containing radon may be implanted in a tumor or applied to the skin surface, or used in any way in which radium itself might be used. Histologic changes induced by radon were described by Melnick (?)(Chi 13: 84, 1940). Radon ointment can be used (Isaak, ADS 45, 840, 1942; Eadmow, JID 61: 316, 1939). Dosage was fully discussed by Quimby and Desjardins (J 112: 1033, 1939).

[When radon ointment is applied to the skin, there occurs considerable exhalation of radon from the lungs (Lange and Evans, Radiol 48: 514, 1947).]

Mesothorium is a radioactive substance in the thorium series. Thorium X bears the same relation to mesothorium that radon bears to radium. Its half value period is 3.64 days. It can be incorporated as ointment or liquid preparations and applied to the skin in the treatment of telangiectasis, eczema, psoriasis or other conditions. The activity of thorium X

is expressed in electrostatic units per cc. of the vehicle. With a solution in alcohol diluted to 100 to 250 esu per cc, Tinkus (JID 12: 41, 1949) reported benefit in seborrheic dermatitis, psoriasis and pruritus ani.

See also Coral (Lancet 1: 316, 1953), Sher and Howes (Radiol 56: 39, 1951), Lewis et al. (RockyMtMJ 49: 753, 1952), Witten et al. (JID 21: 249, 1953).

Radioactive Cobalt is comparatively cheap and effective in needles used as radium needles are used (Myers: Sci 107: 670, 1948). The gamma radiation from radiocobalt is monochromatic, needs no filtration, is easier to handle in designing apparatus than radium, gives no gaseous disintegration products, and is rapidly eliminated, if absorbed, rather than stored in the body. Its short half-life necessitates continual recalibrating.

See Warren (J 144: 417, 1950), Morrison et al. (Sci 115: 310, 1952), Herman (South MJ 45: 498, 1952), Barkell et al. (BritJRadiol 27: 1, 1954), telecurie therapy.

Radioactive Phosphorus, with a half-life of 14.3 days, emits only beta particles, the maximum tissue penetration of which is 8 mm. Exposures of 24 to 36 microcurie hours per cm produce mild erythema, while about 50 times that dose induces bullous epidermitis (Low-Beer: Radiol 47: 213, 1946). Solutions of P[32] taken by mouth are capable of yielding noteworthy palliation in some cases of lymphoblastoma (q. v.). The effect is inferior to x rays or nitrogen mustard in Hodgkin disease, lymphosarcoma and chronic lymphatic leukemia, though it is especially good in polycythemia vera and chronic myeloid leukemia (Stroebel: PSMMC 29: 1, 1954).

Topical use of radiophosphorus and radiostrontium, which are pure β emitters, was described by Low-Beer (GI 10: 60, 1954) who treated effectively keratoses and basal cell carcinomas by applying to them blotting paper trimmed to shape and soaked with P32 in Na_2HPO_4. The dose may be calculated in microcurie hours per sq. cm., or in r. See Witten et al. (JID 23: 271, 1954), β radiation with Sr90.

Other Radioactive Agents.—See Biological Effects of Beta Radiation (McGraw-Hill, 1951), recording some of the results of research done under the Atomic Energy Commission 1942 to 1946. High-energy alpha particles produced by the cyclotron can penetrate to a depth of 14 cm and force specific ionization concentrated in a narrow sphere near the end of the beam (Tobias et al.: CancerRes 9: 619, 1949). See Biological Studies with Polonium, Radium and Plutonium (McGraw-Hill, 1950) concerning especially the toxicity of radium.

Neutron injury was observed by Stone et al. (Radiol 35: 322, 1940); see Chatters (Sci 87: 262, 88: 231, 1938). The effect of neutrons on animals was attributed to secondary ionizing radiations by Tobias et al. (Sci 107: 115, 1948) and resembled that produced by P32.

The effect of high-energy electrons is mentioned in discussing the treatment of mycosis fungoides (q. v.).

Heat (Hyperpyrexia) as a therapeutic agent has been recognized during many centuries of medical activity. In recent times novel measures for producing and maintaining heat have been developed. More kinds of dermatitis are soothed by cool applications than by hot ones. Fever is thought to be a protective physiologic response although the nature of it is not understood. Since some parasites are killed or damaged by temperatures that human tissues may be able to tolerate, artificial fever therapy has a rational basis. Its status practically must depend on experiment. The means for producing fever is of no matter in itself, it is generally thought.

Methods of producing fever include baths, cradles, cabinets with electric lights in them (Brown et al.: BMJ 1: 67, 1943), electric blankets, medical diathermy machines, induction machines, foreign protein and malaria. Short wave radiation was found to provide simply comfortable warmth for the cultivation of many bacteria when Liebesny et al. (KlinWchn 12: 141, 1933) tested its effects. There is always danger of burns, exhaustion, heat stroke or cardiovascular accident whatever the means used and it should be borne in mind that a cure ought not to be more severe than a disease. Real utility of fever therapy existed in the preantibiotic treatment of syphilis (q. v.) and gonorrhea (Tauber and Goldman: ADS 41: 917, 1940; Krusen and Elkins: J 112: 1089, 1939). Atopic eczema may respond favorably temporarily.

Heat usually relaxes muscles, increases the transudation and rate of lymph drainage and the removal of intracutaneous dye, promotes vasodilation, so increasing the rate of blood flow, and induces temporary leukocytosis. Infra red treatment should last at least 20 minutes and cause erythema. Such radiant or incandescent heat is more penetrating than nonluminous energy which feels hot but penetrates only a millimeter. Conductive heat is least penetrant. It may be obtained with water bottles, baths, pads, blankets or the paraffin bath, which last I have found useless in dermatology.

See Council Report (J 142: 27, 1950) on medical diathermy; Wakim (J 139: 1091, 1949) on physiologic effects of heat and hypertherm therapy; Osborne and Frederick (J 137: 1036, 1948); Krusen et al. (PSMMC 22: 209, 1947) and Editorial (J 139: 928, 1949) on microwave (Radar) heating effects, which induce maximum temperature in the subcutaneous tissues and can blister as well as produce deeply buried burns.

Cautery—The ordinary electric cautery is simple reliable dependable convenient and economical With properly designed points, delicate destructive work can be done. By surface application sufficient only to vesiculate, one can destroy leukoplakia and seborrheic keratoses. Its instant effect on cells probably differs little fundamentally from the slower effect of x rays. See Jacobson and Aleon (ADS 61 842, 1950) Carcinoma treatment (p 1225)

Electrolysis and Ion Transfer—When the poles of a galvanic battery contact moist animal tissue a current passes. Soluble drugs can be introduced into the skin the positive sponge is moistened with the desired solution, the circuit closed, and the current turned on In this procedure the positive pole accumulates acid, vasoconstricts, stops hemorrhage increases tone and ionizes Cu Zn and Cd The negative pole accumulates alkali vasodilates, promotes hemorrhage relieves spasm and ionizes salicylates, iodides and salts.



Fig 71.—Post electric cautery an instrument of simplicity and utmost usefulness t the dermatologist in treating warts, nevi, keratoses and cancer

If a needle is used as the negative electrode and is placed within a follicle hydrogen ions accumulate about it and necrotize the follicular epithelium. This agency is used for the destruction of dilated capillaries and various small growths and is particularly valuable in getting rid of superfluous hairs. The source of current is of no consequence, provided it is direct. A current of 1 0 Ma. is required. Cipollaro (NYSJM 39 1475 1939) pointed out the hazards of unskilled use of this surgical ionization and disparaged as I do the multiple needle technic. Some operators use the high frequency current applied through the electrolysis needle for a brief instant in contrast with the 10 to 20 seconds required by the galvanic current. Great skill is required to prevent scarring (Karp ADS 43 85 1941 Erdos-Brown ADS 46 496, 1942) See Hirsutics (p 1328)

See Baker (APhysTh 20 197 1939) histamine and methylcholine; Abramson and Gettner (JID 4 243 1941) epinephrine Council Rpt. (J 117: 360, 1941) Peyra (ADS 53: 91, 1946) aerosol influence on $CuSO_4$ penetration Frew (ADS 53: 34 1946) treatment of

therm and hyperhidrosis by iontophoresis with CuSO₄: Aarna et al (JID 10: 85 1948) Iontophoresis of Pyribenzamine (Ruhley) pruritus. Abramowitsch (Treatment by Ion Transfer Grune & Stratton, 1946, p. 186)

High Frequency and Fulguration Currents are alternating currents of 10[illegible] cycles or more per second obtained with a spark gap type of generator or a vacuum tube oscillating circuit. High frequency currents may be applied to the skin by means of vacuum electrodes, the resulting odor of ozone may have good psychotherapeutic effects. The high frequency caustic spark refers to the local application of a spark by means of an insulated pointed metal electrode, effective in destroying small cutaneous growths.

Short wave diathermy is used medically for heating, while long wave diathermy apparatus is used for various surgical effects, the energy being concentrated in a small region for the purpose of destruction of tissues.

Three forms of surgical diathermy are employed (Mackee and Cipollaro AMA Handbook of Physical Medicine 1950 p 294). (A) Cutting current or biterminal high frequency current obtained from the primary winding of the high frequency transformer. (B) Electrocoagulation or biterminal (sometimes monoterminal) high frequency current obtained from the primary winding of the high frequency transformer, and (C) Electrodesiccation, monoterminal high frequency current from the secondary winding of the high frequency transformer.

Endothermy and desiccation produce heat by the resistance of the tissues to the passage of the high frequency current. The applicator is cold when applied and is pointed. Accurate destruction can be achieved and the agents are used mainly in the treatment of neoplasms and verrucae. Keloid frequently follows the removal of small tumors by coagulation, especially those located over the sternum. See Cipollaro (ArchPhysMed 34: 621 1953)

Ultrasonic Vibrations are acoustical energy in frequencies beyond the limits of hearing of the human ear generated at high energy levels by the piezoelectric effect of controlled oscillating currents on quartz crystals. Frequencies of wide range possess biologic effects, which are interesting but at this time of limited practical value to dermatologists. Wood and Loomis (PhilosMag 4: 417 1927) were the first to describe biologic effects, while the ability of high frequency sound of about 9,000 cycles per second to kill *B coli* not through the agency of heat was noted by Williams and Gaines (JInfectDis 4 : 485, 1930) and similarly to kill streptococci, by Chambers and Flosdorf (PSExpB 34: 631 1936). Destruction of cells is associated with cavitation, the separation of gas and liquid, apparently outside the cells (Harvey and Loomis JGenPhysiol 15: 14 1931). See Bergmann (Ultrasonics translated by Hatfield, Wiley 1939)

The agent is in common use in research laboratories for mixing and dispersing substances, for fragmenting cells as in the preparation of vaccines and for sterilizing without extreme heat, although certainly extreme heating effects can be obtained (Hamre … t 5 … 70 1949; Nelson et al.: APhysM 31: 6, 1950; Woeber: AfDuS 155: 656, 1950; Schwarz and Carstensen: J 149: 1 1 1952). Templeton (ADS 67: 159 1953) reported interesting experiments in the dermatologic use of the modality. While a wart can be destroyed and cured by ultrasonic energy, the electric cautery is easier. Ultrasonic energy can be used to warm tissues, after the manner of diathermy (Meyer: AnndeD 79: 161 1952) and is certainly capable of doing harm.

See Herrma (ArchPhysMed 35: 200 1954), treatment of scars. Schwartz (SouthMJ 47: 854 1954), in osteoarthritis, peripheral vascular disease, varicose ulcers. Bauer (BritJPhysMed 1 … 97 1954), best effects in cases of neurologic causation. Council on Physical Med Rpt (J 15 … 140 1955), controversial value, applicability not yet limited.

DERMATOSES DUE TO PHYSICAL AGENTS

TRAUMATIC DERMATOSES

The skin is subject to injury by pressure friction, abrasion excoriation bruises, tearing, cuts splinters and the like. Xerotic skins have a relatively thin epidermal layer vulnerable to alkali The ease with which sufferers from epidermolysis bullosa or cutis hyperelastica are injured comprises a significant feature of these diseases. Hair and nails may be traumatized Permanent wave devices may pull a wisp so that parts of the scalp become sore and even temporarily denuded. A long toenail in a short shoe may be blistered loose in walking

Friction Dermatitis occurs in various jobs. The exact method of performing the job must be understood in order to clarify diagnosis and correctional effort (Tulipan and Appel MRec 154 443 1941) Occupational corns, calluses, and stigmas are of this nature (Ronchese J 128 925 1945 Occupational Marks and Other Physical Signs, Grune & Stratton 1948) Injury by siliceous spicules from certain sponges handled by oystermen (Corson and Pratt ADS 47 574 1943) and asbestos corns (Howell and Alden ADS 49 312, 1944) exemplify possibilities Shaving especially shaving against the grain, may provoke troublesome mechanical irritation of the face (Baer UCutRev 4 446 1941) and beard hairs falling onto the skin from an electric razor were reported as behaving like itch powder (Moore ADS 44 69 1941) Clothing is a common cause wool or starch being the usual offender

In infants, the nuchal flexures and medial areas of the thighs are likely to suffer from friction especially with wool starched garments and corduroy Chafing if severe disrupts the *epidermis sufficiently so that oozing and crusting* occur and secondary infection may complicate the situation. The page boy coiffure *may* result in chafing *of* the nape *of* the neck (Shellow ADS 40 91 1939) Compare the disruption of the corneum produced by repeated applications of Scotch tape as noted under Epidermis, separation of

Blisters due to the friction of shoes may sometimes be prevented by covering the skin with a bit of cellophane from the wrapper of a cigarette package (Hamilton)

Patch tests, as Tulipan and Appel pointed out are not helpful, for they do not reproduce the *mechanics of etiology* Efforts to cure such eczema by diet are even farther afield Petrolatum alleviates but cure requires elimination of the cause

Abrasions and Excoriations are recognized by linear discrete lesions where superficial layers of skin have been scraped away Protection and the prevention of secondary infection suffice in therapy After careful thorough cleansing a dressing of petrolatum or tetracycline ointment comfort a floor burn and allows it to heal.

Bruises are colorful because blood has entered the skin from broken vessels. If the accumulation of blood beneath the skin is large (ecchymoma) it may require evacuation, although resorption, if infection does not occur is usually complete. If not complete, organization of the clot takes place with a cicatricial result such as cauliflower ears.

Wounds of the skin require cleansing of edges hemostasis, neat apposition and a protective dressing. Scalp wounds rarely become infected. Débridement may be necessary if a crushing injury of the skin is untidy To minimize the scar of an elliptical excision held together by fine silk sutures, the sutures may be removed after 24 to 48 hours, applying Scotch tape to the wound to support it for the next few days.

Splinters may be of various sizes and materials going at the skin at various angles and to various depths. Good light magnifying glasses, pointed scalpel and needles and fine forceps aid greatly in their removal Wood and glass are not visualized by x rays. Glass spicules especially may be difficult to remove. One may wait, with aseptic protection, for the eventual purulent foreign body reaction until the splinter "festers out" when it

can easily be reached or expressed. *In getting at a fragment of wood or metal, a precise cut made obliquely toward the pathway of the splinter from beside it may have to penetrate only the corneum to enable one to grasp the splinter.*

Trichome Dermatitis is due to irritation by spicules, hairs and scales of the epidermis of plants, particularly the cow itch *tree of Australia (Laurence: MJAustral 2: 16 1935)*. Itchy papules on the extremities provoked by barberry thorn comprise another type of foreign-body dermatitis (Schwartz: ADS 37: 8 , 1938). Compare Browntail moth and Schistosome dermatitis.

Glass Wool and Fiberglas.—See Dermatitis venenata, *Industrial (p. 120)*.

Fracture Blisters.—Bullae may develop at the site of trauma in cases of fractures due to blunt injury accompanied by soft tissue damage (Buckley and Lobitz: NEngJM 249: 11 1953). They appear as early as 11 hours or as late as 5 days afterward and are due to simple separation of the epidermis from the dermis.

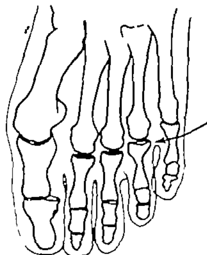


Fig 7.—Corn



Fig 3.—Callus (Dr Sam Sweitzer)





Figs 14 and 15.—Soft corn, attributed to pressure of bony spur on proximal end of proximal phalanx of fourth toe. (M ey PBMAC 15 610 1940.)

CORN

Corns are circular circumscribed slightly elevated hypertrophies of the horny layer cone-shaped with the apex pointing inward. Corns occur on the toes or other *places exposed to friction and pressure*. Generally smaller and more sharply circumscribed than calluses, a corn is distinguished by the presence of a horny core or tap the deep end of which presses on the tender cutis. Hard corns occur on exposed surfaces, and their tops are rounded and burnished. Corns arise as the result of pressure or friction, usually from ill fitting shoes. Orthopedic disorders often play an important role. Some occupations cause corns to develop. Occasionally a corn ulcerates because *of infection or pressure necrosis*.

Asbestos spicules may produced cornlike foreign body reactions (q v Howell ADS 49 312, 1944)

Corns are distinguished from warts by shaving off the excess keratin carefully so as to expose if present the tips of the elongated dermal papillae which characterize verrucae It is a grave error to give to a corn the large dose of x ray therapy which will cure a plantar wart.

Soft Corns develop between the toes and as a result of maceration and mycotic fermentation are soft moist and grayish. They are clinically rebellious lesions, attributed to mycotic infection primarily by Weidman (J 90: 499 1928) In treatment I know of no remedy more effective than Freezone an ether solution of salicylic acid in collodion mainly Circumspect applications of dichloracetic acid have cured several patients of mine The shoes should be wide toed and lightweight

Seed Corns are circumscribed plantar dyskeratoses which can be picked out only to recur They are not traumatic corns, verrucae arsenical keratoses, or punctate keratoderma but perhaps are volar seborrheic keratoses. Compare Verruca Plantaris.

Treatment.—The basis of successful treatment is to remove the cause The adoption of broad toed foot form shoes made of soft leather will often prove curative Orthopedic consultation and correction may be required. The lesions can be trimmed neatly with a sharp blade and removed temporarily by the use of 40% salicylic acid plaster A chisellike instrument is especially adapted to the trimming of corns, after which the cavity is painted with tincture of iodine See Filer (AmJS 29 444 1935) Thick sponge rubber soles worn exclusively for three months will cure corns, according to McFarland (ADS 67 278 1953) who described the thickening and loss of pigment of areas subject to pressure and friction and discussed the interrelationship of psychic disorders with mechanical lesions.

CALLUS

Symptoms.—A callus is a hyperkeratotic plaque due to chronic intermittent pressure and friction. The sites of predilection are the volar surfaces. The lesions are yellowish or brownish with slightly elevated, burnished surfaces. At the circumference they merge into normal skin Often occupationally determined they are seen on the hands of mechanics, blacksmiths, metal workers, stokers and oarsmen, on the fingers of harp and violin players and even on the lips of trumpeters. Bilateral calluses from friction are seen on the dorsa of the thumbs of leather buffers (Warren J 114 571 1940) The four brothers reported on by Mueller and Sugar (J 122 743 1943) who had the calluses under the great toes with ulceration were in fact sufferers with familial syringomyelia. Calluses do not arise spontaneously See Keratoderma climactericum some callused feet improve when the patient is given thyroid estrogen or cortisone.

Treatment.—The lesions are likely to undergo fissuring which is painful. They can be temporarily removed by applications of 20% salicylic acid in an ointment vehicle or by careful shaving Permanent relief can be secured only by removal of the cause, which may require orthopedic consultation.

SCAR

Symptoms.—Cicatrices consist of new connective tissue which replaces mesodermal discontinuities caused by trauma or disease. They are whitish or pink, and firm or atrophic in consistency Their outline approximates that of the lesions in which they develop Their surface may be depressed below the level of the surrounding skin, atrophic scars, the surface may be on the plane of the skin or it may be elevated, hypertrophic scars. Neatest cicatrices are those resulting from clean incised wounds when the edges have been held together In variola, syphilis, and herpes zoster the lesions are atrophic, white and soft. Hypertrophic scars develop as a rule from burns and following deep lacerated or infected wounds. They never extend beyond the



Fig. 76.—Sc f xten i third degree burns



Fig. 77.—Sca of old burn.

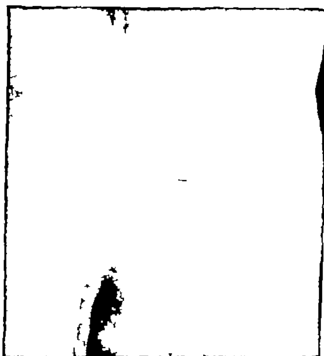


Fig. 78.—Atrophic stria of lumba region, seen in an adolescent (Wiener Skin Manifesta tions of I ternal Disorders, Mosby 1947.)

boundaries of the original injury a feature which distinguishes them from keloid Symptoms are commonly absent If present they are usually burning, prickling or formicating in character and due to nerve filaments that are caught in tiny amputation neuromas (Kredel Surg 8 98 1940) Scars tend to contract mainly in the diameter perpendicular to the lines of cleavage Occupational scars are seen on the right thigh of the right handed shoemakers from slips of the knife (Schwartz)

Treatment.—Irregular or hypertrophic disfiguring scars can sometimes be excised. The surface can be rendered smoother and less conspicuous by the use of solid carbon dioxide x rays or radium Blistering doses of ultraviolet irradiation diminish the conspicuousness of shallow scars it is thought (Fisher J 110 642, 1938) Methods of peeling the skin and the good results claimed were discussed by Eller and Wolff (J 116 934 1941) The surgical treatment of scars from burns, including those which are painful depressed, thick, thin and unstable or keloidal, was discussed by Davis (J 125 621 1944) The painful scar may be rendered painless not for a brief period but for a long time by infiltrating it with procaine (König DentMWchn 64 1872, 1938) See also Acne treatment

ATROPHIC STRIAE (STRIAE DISTENSAE)

Sharply defined linear atrophic lesions are often seen over the abdomen lower back, breasts flanks or lateral aspects of the thighs. Their disposition parallels the lines of cleavage and they are generally grouped in such a manner as to suggest that the skin has been overstretched They are sometimes red in color particularly in the early stage but they become whiter than the adjacent normal skin. The lines are slightly sunken They are without pain or tenderness.

These lesions symptomatically follow mechanical overstrain, as in pregnancy (lineae gravidarum) tumors, obesity and ascites. There is also a type which is apparently idiopathic, but the possibility that the lesions have been caused by either trauma or overextension can seldom be excluded. A common site is the lumbar region in young people Rosenthal (Lancet 1: 857 1937) denied in these cases a relation to posture The condition occurs in a period of rapid growth in adolescence and extreme flexion of the spine in the course of everyday life overextends the skin of the back, which may be presumed in these patients to be less than sufficiently elastic Both cases of Weber (Lancet 2 1417 1935) had their onset at puberty Among 834 feeble minded persons striae distensae were found by Butterworth and Wilson Jr (ADS 39: 703, 1939) in 39 and of these 30 had undergone rapid gain in weight. An association with steroid activity was postulated by Sisson (JPediat 45: 520 1954) who noted the common association of acne in his adolescent cases and who reported an incidence of 25% in 100 healthy children some of whom were preadolescent

Astonishing striae may be seen in basophile adenoma of the pituitary (Cushing J 99: 281, 1932 Hall et al.: Lancet 1 802, 1939) Schilling (MWelt 10: 259 1936) thought them to be a sign of hyperfunction of the pituitary anterior lobe though Cushing attributed them to the rapidity with which obesity is acquired. The administration of ACTH (see Dermatitis Medicamentosa) causes striae when it causes Cushing's syndrome

Their appearance in the patellar region in children who were recovering from severe illness, such as typhoid fever has been noted by many authors (Shepherd JCutDis 8 436 1890; 9 89 1891; Northrup TransAssnAmPhys 18: 197 1903; Bunch BJD 17 1 1905) Weight gain as well as weight loss may occasion their development. Among the tuberculous patients of Macrae Gibson (BJD 64 314, 1953) those who showed red lineae distensae were the ones who had gained on the average 4.7 lb. per month, while those who had gained only 2.2 lb. per month did not show the lesions, for the most part A tuberculous patient who became nephrotic was given ACTH, in desperation, suffered rupture of the belly wall through such a stria (Lawrence et al.: J 152 1526, 1953)

Pathology.—Bunch found alterations in the elastic tissue characterized chiefly by the distribution and new parallel arrangement of these fibers, the rearrangement having been brought about at the expense of the transverse elastic fibers which had ruptured and retracted to the edge of the lesion At the margins of the lesions the elastic tissue appeared denser than normal, probably a result of the presence of the broken, retracted fibrils. Rupture of elastic fibers seemed probably due to gradual stretching or tension rather than to inflammation Elbert (ADS 43 635, 1943) found, in the early stage of hypertrophic striae distensae, productive inflammatory changes with degeneration of elastin, and he propounded the theory that the toxic agent in these cases may be a product of a disturbance of the endocrine system. In discussing the paper Pusey emphasized the fact that there is a mechanical factor in the vast majority of these cases.

Treatment.—Nothing can be done to cure the lesions, which are permanent. Proper support to prevent overstretching of the skin may keep them from developing during pregnancy (Aagaard ActaOb-Gyn 28 1 1949)

See Rothwell (JCutDis 3 : 210 1919) case; Milian (ADS 1: 481 19 0) case; Hodel and Walter ([illegible]) 231: 182, 19 1); Allmendi ([illegible] 11 24, 1937) incidence 45% in tuberculous patients; Musser (AfDus 177: 732, 1938) White (ADS 31: 439 19) 1st girl.

THERMAL INJURIES BURNS AND FROSTBITES

Erythema.—See Erythematous dermatoses of undetermined cause

Erythema Caloricum and Erythema Pernio (Chilblains) are erythemas due respectively to heat and cold. The effects of radiant heat such as the long-continued application of an electric pad produce erythema ab igne In this condition, there is often accompanying inflammation and pigmentation is usual. Chilblains are purplish infiltrated lesions which develop on the nose ears heels, and other prominences as a result of repeated exposure to cold They are common in damp, cold climates, such as that of London, and occur especially in persons who habitually suffer from cold hands and feet, and who are said to have *chilblain circulation*. *Marmoraceous redness of* the arms and legs, more pronounced on the dorsal surfaces, is notable in many persons especially those who are long accustomed to being not warm enough The skin is cool and puffy and it may become hypertrophic to a degree that justifies sympathectomy which results in vasodilation warmth and relief See Pernio





Fig [illegible]—Erythema ab igne marmoraceous appearance induced by hot pad
Fig [illegible]—Frostbite, showing results t telangiectasis. (Dr Stuart Way)

Burns range in extent and severity from slight localized redness to widespread tissue necrosis. They may be divided according to severity (1) burns of first degree characterized by the presence of the inflammatory signs of heat, pain, redness and swelling due to *necrobiosis of epithelium and superficial vessels* (2) burns of second degree characterized by these symptoms, plus vesiculation and exudation due to epithelial necrosis (3) burns of third degree, including all thermic injuries of the skin which result in necrosis of both epithelial and connective tissue substance Primary shock in extensive burns *is like other surgical shock, and* is to be treated with plasma, blood transfusion, dextrose oxygen, sedation, heat and perhaps adrenal cortex extract (Harkins J 119 385 1942) In burns that destroy nerve endings, pain may be wanting but shock appears in a few hours. In severe burns the patient should be treated for shock at once whether he shows it or not Aldrich (NEngJM 217 911 1937) stated that delayed shock which comes on after from 10 to 20 hours, attributed to histamine by others, is simply inadequately treated primary shock the viscosity of the blood is increased even more in capillaries than in veins, so that the patient suffers erythrocytic

emboli, which cause fatal anuria ulcerative colitis, and focal necrosis of adrenals, lymphoid tissue heart muscle and other organs. Intoxication which comes on still later Aldrich thought to be bacterial intoxication, although this is open to question (McClure J 113 1808 1939) It may be prevented by maintaining bacteriostasis of damaged areas. Pyemia, erysipelas and tetanus are among the complications one anxiously avoids. When vibrissae are burned, look out for laryngeal and tracheal involvement, include high humidity in therapy and be prepared for tracheotomy When nails are blistered off digits are usually lost

Standardized thermal injuries were applied to various parts of the body by Benjamin and Cornbleet (ADS 68: 530 1953) Down the leg from knee to ankle they found a gradient of diminishing rate of healing, but this was not evidenced when the patient remained abed. Bed rest reduced the absolute time of healing which was apparently affected by gravitational factors.

Controlled thermal injury was investigated experimentally by Williamson and Scholtz (JID L: 41, 1949) with special reference to the injury necessary to incite blister formation. Blisters always resulted when heat of 146 F was continued for 10 seconds. If 122° was applied for 10 minutes, the interval before blistering appeared might be as long as 4 hours. *The histologic changes in the basal cells were found to be typical.*

Burns in Children are tragic and largely preventable. The causes were studied by Bleck (J 158 95 1955) who listed (1) ignition of clothing from such sources as fireplaces, trash fires and stoves, in 159 cases; (2) direct contact with flame as falling into fireplaces in 8 cases; (3) gasoline and kerosene fires, in 51 cases; (4) hot liquid burns, as from pulling a kettle off a stove in 9 cases; and (5) miscellaneous causes, in 4 cases. Education of all persons who care for little children should result in the prevention of a high proportion of such accidents.

Cosmeticians Burns.—Deep little burns are often caused by inept use of permanent wave machines. Severe burns can result from ignition of celluloid combs.

Electric Burns.—Next to bone, the skin offers greatest resistance to the passage of electricity since the greater the resistance the greater the burn, severe skin burns are *common, especially of the hands. With voltages of from 5,000 to 10,000 charring is* swifter and more definite than with lower voltages, which generally cause tissue damage not immediately manifest as desiccation or charring Relatively small skin damage may coexist with serious injury to deep structures, particularly tendons and their sheaths, so that sometimes what appears to be a superficial injury evolves as a grave and far reaching one. The *customary classification of burns as to degree is not appropriate in describing* electrical burns (Edwards and Bowles AmJSurg 47: 299 1940) See Electric burns of the mouth.

Hydrofluoric Acid Burns are comparatively painless for several hours despite deepening necrosis. They are best treated by applications of sodium bicarbonate solution and magnesium oxide paste, injecting under them 10% calcium gluconate to stop their progress (Jones JIndustHyg 21: 205 1939)

Phosphorus Burns *are extremely painful and slow to heal because of the formation* of P_2O_5, which combines with tissue fluid to make phosphoric acid. Emergency treatment requires immersion in water or wrapping with wet blankets to smother the fire, later picking out bits of phosphorus while swabbing with warm 5% solution of sodium bicarbonate. Copper oleate, prepared from the sulfate mixed with soft soap, inactivates by combining with phosphorus to form copper phosphide (McCartan and Fecitt BMJ 2: 316 1945).

PROGNOSIS.—Of 1,574 burns, *death was the result in 8.2% of those due* to scalds, 31.2% of those due to ignition of clothing and none in those due to contact with flames or hot solid bodies (Lütken UgeskfLaeger 20 409 1937) The outlook depends on promptness and effectiveness of treatment, as well as extent of injury Of 250 burned children, all who lived to the tenth day survived 14 deaths occurred, pneumonia topping the list of contributory causes (Lavender J 118 344 1942) Among 8 000 deaths reviewed by McClure (J 113 1808 1939) *almost half involved children under 6* years of age and four fifths of these were preventable. Loss of plasma protein was important, also tissue anoxia due to hemoconcentration and circulatory failure. *Liver cell damage perhaps due to absorption of toxin formed in the* burn, was conspicuous. The possibility of recovery is to some extent inversely proportional to the area of the burn Berkow (ASurg 8 138 1934) estimated the area in adults of head 6% upper extremities 18% trunk including genitals 38% and lower extremities 38% Of the lower extremities, the feet comprise one-sixth, the legs one-third, and the thighs one-half. In children under 12 years, the head is larger and the lower extremities smaller Burns exceeding 50% of the surface are extremely grave.

If metabolic demands of the tissues are met, shock adequately treated, hemoconcentration corrected (hematocrit kept under 50), rigid asepsis maintained and toxicity successfully combated, the outlook is favorable (Pemberthy and Weller, SGO 74: 428, 1942).

Intravenous injection of fluorescein sodium, 10 cc. of 20% solution, followed by illumination in ultraviolet light distinguishes second degree burns which glow yellow from third degree burns which look purple or black (Dingwall and Andrus, AnnSurg 120: 377, 1944).

TREATMENT.—For small burns, soothing and protective lotions such as cool moist packs and petrolatum are all that is needed. In burns of second degree the vesicles should be incised and drained aseptically, loose epithelium removed and an antiseptic dressing applied. Tetracycline or bacitracin ointment or sterile petrolatum gauze may be recommended. Butesin picrate is unsatisfactory because eczematous reaction to it is common.

In the treatment of severe burns, the surgical principles according to Allen and Koch (SGO 74: 914, 1942) are (1) prevent and combat shock, (2) convert an open contaminated wound into a clean one, (3) cover the wound with the simplest possible dressing which does not increase tissue damage, does allow for drainage, exerts uniform moderate pressure and is easy to remove, (4) keep the injured parts at rest and (5) secure healing with the minimal loss of function and of time. Restlessness and rapid pulse are constant and important signs of fluid loss and indicate the immediate need for plasma. The administration of oxygen is a valuable adjunct to treatment. The most important source of infection is the mouth of the person who treats the burn and this must be masked. Soap and sterile water aseptically used are best for cleaning a dirty burn, and fine-meshed gauze sterile and impregnated with petrolatum is the best dressing. It is covered with mechanic's waste or sponges to provide a resilient covering held in place by a retention bandage that furnishes even pressure without constriction.

The blister fluid contains about 75% as much protein as the blood plasma and plasma must be restored adequately. Freeman et al. (J 122: 924, 1943) would give at once 50 cc. for each 1% of body surface burned, 40% of this amount later during the first 24 hours and an equal amount within 72 hours.

Swelling, which accounts for great loss of protein and fluid into the interstitial spaces, may be controlled with pressure bandages or even plaster casts (Levenson and Lund, J 123: 272, 1943; Harkins, J 125: 533, 1944).

In attempting to control infection, one (1) blocks admission of pathogens to the burned area at the time of doing dressings and (2) blocks their entrance between one dressing and the next (Colebrook et al., Lancet 1: 893, 1948). A trained team can do these things, for asepsis requires masking and education of personnel who handle burned patients, as well as proper bandaging and strict attention to detail. Antisepsis with antibiotics is also essential.

Azotemia occurs early and usually is reversible as urinary output approaches normal, but in some severe cases it does not disappear. Hypoproteinemia and inversion of the A/G ratio must be watched for and are met by increasing alimentation (Taylor et al., NEngJM 229: 855, 1943).

The value of cortisone in burns is debatable and so to be adjudged not conspicuous. Whitelaw (J 145: 85, 1951) thought ACTH afforded excellent support in 4 cases. Plastic surgeons at this time are not enthusiastic.

For extensive burns, Davidson (SGO 41: 202, 1925) recommended aqueous solution of tannic acid applied by spray. Coagulants other than tannic acid can be used. Dyes, such as gentian violet, are useful, but Cohen (BMJ [illegible] 251, 1940) found in war experience that tannic acid and silver nitrate are preferable. The eschar produced by tannic acid is inflexible [illegible] to curl at the edges, and infection [illegible] not readily be detected beneath it. [illegible] kept [illegible] is more likely to occur in deep burns and may have its onset [illegible] 7 days. [illegible] wet dressings [illegible] time [illegible] be preferred in small second degree burns. Blisters [illegible] 4 hours before tannic [illegible] already infected and should not be so treated. Burns of hands and fingers should be treated with a grease, not with tannic acid (MacCollum, J 116: 2371, 1941). Tannic acid [illegible] now days [illegible] doing more harm than good, though [illegible] infection spreads under the eschar and intoxication with liver damage occurs (Lee and Rhoads, J 125: 610, 1944).

Continuous bath treatment wa described by La ender (AmJSurg 45: 534 1939) Continuous irrigation of the b rned part within an enveloping bag wa recommended by Pearson et al. (BMJ 1 41 1941)

A casein gel treatment was advocated by Curtis et al. (J 147: 41 1951) The partially hydrolysed casein on the burned area is covered with gauze impregnated with zi c acetate and it form a semipermeable membrane which prevent exudative protein loss and supports the damaged capillary bed, providing splinting and relief of pai It enables early grafting minimizes infection and is simple in application.

Acid débridement wa invented in the search for means to selectively digest and remove th necrotic slough. Pyruvic acid 8% in cornstarch paste at pH 1.0 was said to clean slough in 4 days so that grafts could be applied early (Conn r and Harvey: Ann Surg 120: 362, 1944) Pyruvic acid, 0.9% (0.1 molar) in starch paste wa studied by Sulzberger et al. (AnnSurg 1..5: 418, 1947) and adjudged safe simple and practical, capable of hastening granulation. Phosphoric acid, 0.1 molar likewise maint ined a pH of 2.0 and was effecti e In a water-soluble vehicle 0. molar phosphoric acid was used by Schweitre and Brad her (NEngJM 44 0. 1951) Its application caused burning pain for from 15 to 30 minutes, controlled with Demerol A dam of petrolatum impregnated felt strips wa used to prevent the mixture from seepi g away and petrolatum strips and fluffed gauze covered the phosphoric acid gel. Dressings were changed ea h 4 to 48 hours, and separatio of the lough was hastened mechanically Epith lium apparently wa not damaged, and areas encompa ing first, second an l third degree burn could be treated beneath the same dressing

Unde some circumstances, the entire burned rea should be excised. A patient may be placed und r a cradle with electric light a the source of radiant heat and the tire rea i covered with sterile gauze kept wet with hypertonic saline

To meet adequately the emergency of a disastrous fire is a terrible responsibility By way of being prepared to do so one will profit from studying the report of Cannon (Surg 15 1 8 1944) co cerning the famou Coco nt Grove tragedy See Enyart and Miller (J 135: 93 1953) on disaster management of the xplosion and fire occurring aboard the U.S.S. Ben i gton 31 \ 26, 1954 util zing the exposure treatment and electrol te replacement by the rule of 9 the surface area of the head a d neck i 9% of the total body surface each upper extremity i 9% each lower extremity i 18%, and the front and back of the trunk are each 18% the remai ing 1% being ccounted for by the genitalia an l perineum. The Hell ood fire resulted in pneumonic death in 13 newborn babies w thin 3 days afterward, reported Cox et al. (BMJ 1: 94., 1953)

Flash burn from explosion may be serious and are common in war A protective cream ha value (B lIUBAMD 76: 7 1944)

The prevention of burns and sc lds which occur i d about the home was of concern to Colebrook and Colebrook (Lancet : 181, 1949) Ed cation of the public plays an important role in preventive efforts, as well as good design of hazardous grates and appliances.

Injuries Due to Cold are called cryopathies or frostbites, and they include trench foot immersion foot chilblain and pernio They may be of any degree of severity acuteness or chronicity and extent of involvement Lewis (BMJ 2 795 837 869 1941) described the effect of light freezing as productive only of transitory local erythema. Exposure of the skin to −10° to −15° C. for 20 seconds induces redness followed by itching and swelling and a wheal typical of the response to acute physical injury The wheal subsides in a few hours, to be followed by local redness and tenderness for about a week, with peeling Exposure to −15° for 60 seconds results in blistering within an hour or two Severe freezing induces necrosis due to vascular thrombosis which appears within a few hours.

Early symptoms of frostbite may be absent, but it is usual for painful burning sensations to be followed by numbness Symptoms are related to the temperature the duration of exposure and the medium in which the exposure took place In high-altitude flying anoxia combines with cold to increase the destruction of tissue Blanching and vesicle formation pallor and coldness, bluish discoloration due to venous congestion, and necrosis and gangrene are seen. Late sequelae well described by Shafer and Thompson (AD 72 335 1955) are pain hyperreactivity to cold hyperhidrosis and various dermatologic orthopedic and neurologic changes.

CLASSIFICATION of cold injuries was given by Pratt (OP 7 34, 1953)

FIRST DEGREE FROSTBITE.—The part subjected to cold for a short time, or to a lesser degree f cold for a longer time hows erythema a d spasm with burning and tingling sensations, and recovers without loss of tissue although there may be some peeli g.

SECOND DEGREE FROSTBITE.—Actual tissue destruction takes place usually limited to skin. Anesthesia and paresthesia accompany marked reactive hyperemia, and wheals and superficial blebs occur. Secondary infection may increase the tissue loss.

THIRD DEGREE FROSTBITE.—These are reactions to extreme cold. The parts do not recover completely, subcutaneous tissues are damaged, extensive injury may be fatal and tissue loss varies with trauma, secondary infection and effectiveness of treatment.

FOURTH DEGREE FROSTBITE.—The injury includes loss of muscle and bone.

FIFTH DEGREE FROSTBITE.—Anoxemia and stress exposure produce deep freezing, the skin being shiny and tense with subcutaneous hemorrhages. The main attack on such problems is by means of prevention.

PATHOLOGY.—There are both cellular injury and local ischemia due to *clotting in peripheral vessels, Pratt believed. Gangrene when it develops, is* of a cyanotic avascular type leading to black, dry necrosis perhaps glove-like and requiring to be split along the fingers to prevent constriction. Secondary infection capable of altering the picture completely is of great importance. *There can be no single pathologic description of frostbite just* as there is no set picture in a burn. Friedman (AmJClinPath 16: 634, 1946) found no essential difference between the pathologic lesions of trench foot and of high altitude frostbite.

Frost Injuries in Warfare were well described by Lieberman (NYBJM 44: 115, 1944) who listed types: erythema and edema, blisters, superficial gangrene, gangrene of skin and subcutaneous tissues, gangrene of an entire acral part, injuries to deep tissues with or without accompanying skin lesion, and chronic relapsing cutaneous manifestations such as chilblains and other forms of erythrocyanosis. Frostbite at high altitude depends in *part on vasospasm and anoxemia, for fingers are more susceptible than cheeks (Davis et* al. BGO 77: 561, 1943). Shelter foot was seen in London in 1940 and 1941 among individuals who sat up all night without compensating rest in the horizontal position during the day (Greene, Lancet 1: 303, 1940; 689, 1941). Swelling of the feet was painless at first, and spread up the leg. It did not occur in wardens who, though exposed to equal cold and damp, were frequently on their feet. Shelter foot, immersion foot and trench foot are basically similar.

Immersion foot (trench foot) occurs when the feet are long exposed to cold and wetness. This may develop even when the temperature is above freezing. Dilation and engorgement of vessels of skin and subcutaneous tissues occur along with agglutinative thrombi composed of red cells and platelets (BullUSAMD, Feb., 1945). Numbness is accompanied by swelling and waxy white areas with scattered cyanotic spots. Swelling increases rapidly when the parts are warmed when redness, hyperemia, bounding pulse within the parts and intense pain supervene. Depending on severity of injury, blebs which may be bloody and ulcerations develop, tissues may turn black, and dry or moist gangrene becomes manifest (Webster et al.: JB&JS rg 4: 655, 194). Recovery may be complete or chronic neuralgic pains may begin or hyperhidrosis with soggy fragility of the epidermis may be a sequel, along with hypesthesia.

Late sequelae are fairly common, including chronic peripheral vascular disease, subjective cold, eczema and plantar ischemia (Fausel and Hemphill, BGO 81: 50, 1945). Sympathectomy may then be desirable (White, NEngJM 228: 11, 1943). The indications for *sympathectomy according to Shumacker and Abramson (AnnSurg 1..3: 902, 194)* who reviewed the effects of the measure as performed on 49 of 100 Mayo Clinic patients, include extensive gangrene, excessive sympathetic tonus, and pain on weight bearing. It is not appropriate in the majority of cases. See Goldstone and Corbett (BMJ 1: 19, 1944); Ungley et al. (BJSurg 33: 17, 1945); Southworth (NEngJM 233: 673, 1945.

PREVENTION OF FROSTBITE.—Elderly persons and people with diabetes or arteriosclerosis must not be allowed to suffer overexposure. Clothing should be carefully planned and adequate and the extremities especially must be protected. Men working out of doors in cold weather should be required to enter *shelter and warm up periodically* and hot drinks are helpful (Brahdy, J 104: 529, 1935; 108: 369, 1937).

In military life discipline must be enforced with respect to extra pairs of dry socks and shoes, the avoidance of remaining long in a cramped posi*tion and the necessity for keeping moving. Water collects within watertight* boots, which are not satisfactory. The avoidance of trauma as from vigorous massage, must be taught and enforced. Bodily cleanliness diminishes the liability to infection, which can greatly increase the damage of even a minor *frostbite.* Frequent inspection is requisite. Loose clothing, the horizontal sleeping position and limited duration of exposure contribute to the welfare of those who must be exposed.

TREATMENT OF FROSTBITE.—The immediate care of cold injuries is extremely important. Further exposure to cold and wet must be ended. Cases with tissue destruction must be put at strict bed rest. Treatment for shock must be instituted, and Pratt approved of whiskey as a vasodilator. Nicotine must be prohibited. Dirty wounds must be cleansed and the cleansing procedure must avoid trauma. Prevention and control of infection require the early use of antibiotics, cultures and sensitivity tests. Sterile dry dressings are advised and the use of ointments is frowned upon as increasing the liability to moist infectious gangrene.

Overheating of frozen tissues is a grave error but debate has not as yet been settled whether the parts should be warmed gradually or brought up to body temperature more promptly. Rapid warming but not heating seems to be gaining approval (Edit. J 148 940 1952). Pratt favored a temperature of 65° to 60° F., pointing out that vascular damage with stasis and edema, is reasonably treated by preventing the delivery of more blood to the part than can be drained from it. Cool therapy relieves pain. It was observed that patients would themselves put their injured parts out the window to obtain comfort and many stated they suffered less in lifeboats on the sea than when put into warm surroundings.

In rabbits experimentally exposed to acute severe frostbite rapid thawing appeared to increase the severity of tissue damage, edema, pain and gangrene reported Arena and Blair (Surg 37: 175, 1955). Ice crystals in the tissues of hamsters did not necessarily result in gangrene but if the frozen tissues were beat, then gangrene resulted (Smith: Lancet 1: 1-55, 1954).

The frostbite cases of Edwards and Leeper (J 149: 1199 1952) occurred in military personnel, whose acute stage of freezing thawing exudation and initiation of necrosis had already taken place. The subacute stage was marked by resolution of necrosis and the commencement of vasospasm and acrosclerosis. In these patients, relief from chilling had been denied, so that vasoconstriction from refrigeration was abetted by hunger, exhaustion, anxiety, blood loss from wounds, hemorrhage and shock, and tobacco smoking. Superficial necrosis was always more extensive than underlying gangrene, and observation for several weeks was necessary before any amputation was performed. It was not possible to predict accurately which patients would show long-lasting effects, but these authors suggested that waiting two years for spontaneous disappearance of symptoms would be ample before performing sympathectomy.

Anticoagulant therapy probably ought to be instituted early. Heparin was used in experiments performed by Lange and Loewe (SGO 82: 256, 1946) and appeared to save tissues which otherwise would have been lost. Lange et al. (PSExpB 74: 1, 1950) prevented red cell sludging and diminished the extent of gangrene as compared with control animals when they used heparin at once in such dosage as to keep the coagulation time 22 minutes or longer all the time for at least 5 days. Pratt advised giving heparin 50 mg. intravenously at once, along with 30 to 70 mg subcutaneously. Testing coagulation time 3 hours later, more heparin in doses of from 30 to 70 mg. should be given subcutaneously so as to keep the coagulation time between 20 and 30 minutes. An oral anticoagulant (Tromexan 1,200 mg. or Dicumarol 400 mg.) should also be given. After the first 24 hours, oral anticoagulant therapy was continued (Tromexan 600 to 900 mg. Dicumarol 300 mg.) to keep the prothrombin time some two to three times the normal. Pratt would continue such therapy for some 3 weeks, or until the fate of the part has been determined. Hemorrhagic complications, the urgency of a surgical procedure or any other contraindication can be met with specific drugs (protamine for heparin, vitamin K for Tromexan or Dicumarol) so as to stop their action.

The period from the second to the twelfth week is of utmost importance to the patient, Pratt stated. The extremities should be kept dry, clean and exposed to air without weight bearing until the wound is healed or separated. Antibiotic and anticoagulant therapy continued. Sterile saline soak for an hour a day will aid a separation of sloughs. Chemical sympathetic blocking agents such as Priscoline or tetraethyl ammonium chloride may be helpful and Mephenesin, by relieving smooth muscle spasm, is useful in controlling pain, often preferred by the patient to opiates. Early sympathectomy does not prevent or limit the extent of gangrene, according to Isaacson and Harrell (Surg 33: 810 1953); its applicability is to the late sequelae particularly.

Vasodilation may be obtained with Hexamethonium, which was considered by Mowrey and Farago (M Surg 110: 249 1952) to be as effective as lumbar block. The technic of sympathetic block was given by Simmons (BMJ 2: 884 1945). Block induced early in the course of frostbite brings about cessation of pain, rapid subsidence of edema, more active circulation, quicker demarcation of nonviable tissues, better granulation and faster healing, according to Shumacker (SGO 93: 727 1951). Sympathectomy is to be considered on the basis of the response to sympathetic block.

The guiding surgical principle in treating frostbite is restraint. All authorities agree that amputation should be delayed, even for three months, until the situation becomes clear. Early surgery is requisite of course to control otherwise uncontrollable infection and to drain abscesses if they occur. Final surgical therapy involves amputations and grafts. The surgeon is given plenty of time to reach his decisions. Hyperhidrosis and the tendency to macerate, vulnerability to secondary infection and dependent cyanosis are annoyances which may continue for years. Sympathectomy can be expected to help them a great deal.

Pernio (Chilblains).—The pernio syndrome may include the acute form of chilblains, the chronic form of chilblains and perhaps immersion foot or trench foot. According to Allen et al. (Peripheral Vascular Diseases, Saunders, 1946) it seems that a similar mechanism operates in all these conditions and has as its outstanding feature a reaction of the peripheral blood vessels to cold. Clinical features are similar and such differences as occur in the nature and extent of the symptoms and signs are due to differences in severity, length of exposure and variability of vessel response to cold. The single name "chilblains" is adequate to embrace all the manifestations of erythrocyanosis crurum, dermatitis hiemalis and nodular vasculitis, in the opinion of Lynn (SMJ 39: 720, 1944) who denied the value of separating these conditions as dermatologic entities. Yet he emphasized the distinction between acute and chronic chilblains: prolonged and repetitious exposure to cold in persons who are prone to chilblains leads to changes that persist and to pathologic lesions that are irreversible.

Pernio was described by Shaefer and Sanders (JMoMA 38: 159, 1941) as a specific peripheral vascular disease in persons sensitive to sudden changes of temperature. Whether it represents solely a vasomotor reaction of allergic origin or is due in part to chronic inflammation is undecided, but there is some permanent change in the walls of peripheral vessels so that minute vessels are dilated while arterioles are constricted. Wigley (Pract 157: 343, 1945) described mild and severe forms and recommended in treatment improvement of the general health, the administration of cod liver oil and iron, the avoidance of extremes of temperature and adequate protective clothing. Nicotinic acid was recommended by Gourlay (BMJ 1: 336, 1948). Histologic studies were made by McGovern et al. (AmHeartJ 22: 583, 1941).

Acute Pernio is experienced by a child who goes out into the snow or cold wet weather without adequate protection for feet and legs and develops dermatitis characterized by its bluish red color and slight edema in its area of distribution. Intense itching and burning are aggravated by exposure to warmth. The manifestation exists for several days, but gradually fades. Sometimes brown pigmentation persists for several weeks. Rarely purpura develops in the affected region during the acute stage.

Chronic Pernio is seen in susceptible persons who have been repeatedly exposed to cold and in whom develop recurring and chronic cutaneous lesions, which are erythematous, ulcerative and hemorrhagic and which often leave residual scarring, fibrosis and atrophy of the skin and subcutaneous tissues after healing. The lesions usually are active during the cooler months and may subside completely during the warm season, when the diagnosis is obscure because the etiologic significance of cold is overlooked. Such cases have been called erythrocyanosis, Bazin's disease, dermatitis hiemalis and lupus pernio. Confusion has resulted, according to Allen et al. (Peripheral Vascular Diseases, Saunders, 1946) from failure to distinguish this syndrome from tuberculous erythema induratum (q.v.) from which it is differentiated by histologic examination. Compare nodular vasculitis.

The lesions are of various sizes, elevated and horseshoe-shaped, reddish or slightly cyanotic, perhaps vesiculated or ulcerated. On healing atrophic

violaceous scars develop Histologic changes comprise (1) angiitis with intimal proliferation, thickening of the arterial walls, and periarterial and perivenous infiltration of lymphocytes, monocytes and neutrophils, (2) necrosis of the fat panniculus, and (3) chronic inflammatory reaction of the subcutaneous tissues, in which giant cells may be found

The typical patient with chronic pernio, as described by Allen et al. (1946) is a woman who complains of recurring erythematous, and ulcerating lesions of the lower extremities. These made their appearance in adolescence or early adult life, and at first appeared at the onset of cold weather and disappeared during the summer On exposure to cold, burning and itching sensations developed in the affected regions, the lower part of the legs. Red, slightly elevated lesions from matchhead to dime size appeared over the anterior and posterior leg region of involvement and sometimes on the dorsum of the feet and on the toes. Blisters developed on these and the color of the lesions deepened in its violet hue Superficial ulceration ensued with a hemorrhagic cyanotic base but with little exudation. Pain was at first present but later subsided. Healing eventuated within three to five weeks spontaneously and pigmentary residual persisted. When new crops of lesions appeared the procedure was repeated. In such cases crops may appear over a period of several months. During the active stage the lower extremities are cool and slightly cyanotic in a cool environment The legs may be somewhat edematous. Livedo reticularis may be present The peripheral arteries pulsate Evidences of occlusive arterial disease are absent.

Livedo Reticularis is characterized by a local and prominent mottling and blotchy or reticular discoloration of the skin of the extremities, of reddish blue color Williams and Goodman (J 85 955 1925) divided cases into three groups (1) cutis marmorata manifested by mottling of the skin on exposure to cold with disappearance on warming (2) livedo reticularis, idiopathic with bluish red mottling more intense than in cutis marmorata and persisting in spite of temperature changes and (3) livedo reticularis symptomatica in which mottling persists but evidence of some other disease affecting the cutaneous vascular system is also present

See Rheinacher (Surg 13 237 1943), case involving lower extremities cured by lumbar sympathectomy Yorke and Klaber (BJD 61 17 1948) case legs and ankles, with recurrent blisters and scarring, associated with Raynaud's phenomenon Ebert (ADS 49: 219, 1944) resemblance of pattern to lesion resulting from intra-arterial emboles, Becker (ADS 50: 114, 1944) stroking area causes pattern to disappear followed by return of bright red blood, proving pathologic process nonobliterative, Barker et al. (AmHeartJ 21 592, 1941) a peripheral arteriolitis Feldaker et al (AD 72 31 1955) livedo reticularis with summertime ulceration.

Erythrocyanosis (Acrocyanosis)—Almost constant coldness and bluish discoloration of the fingers, hands, toes and feet for many years are the features of acrocyanosis. These changes, while more intense in cold weather persist in a warm environment. The color is deep purple when the skin is cold and red when it is warmer Scleroderma does not develop but swelling and puffiness occur particularly in cold weather and some areas may become painful. Atrophy or ulceration does not take place. No evidence of occlusive arterial disease is to be found Acrocyanosis is distinguished from Raynaud's disease by the persistency of its color change and the absence of pallor In erythromelalgia the region of color change is hotter than normal, while in acrocyanosis such regions are cool. Cyanosis in the presence of occlusive arterial disease is related to ischemia and is not true acrocyanosis.

A bluish red network involves generally the legs being supramalleolar in distribution, and the forearms it is greatly intensified by exposure to cold or friction. Only a small drop in temperature suffices to bring on the appearance of vermilion spots which accompany purplish infiltrates. The causative mechanism probably is partial obstruction of arterial supply due to cold sensitivity for nerve block temporarily relieves the condition. It is likely that vasomotor instability of psychosomatic origin plays a part in causation for cold moist hands and feet, with dependent cyanosis, characterized the sufferers from this disease. In therapy continued warmth, such as that provided by central heating is helpful.

See Ebert (ADS 16 426, 1947), Clouston (CanadMAJ 40 166, 1939); Lewis (BMJ 2 837 1941); Wrong (CanadMAJ 46 520, 1942); Barker et al. (AmHeartJ 21 592, 1941)

ACTINIC INJURIES

Sunburn is a common symptomatic erythema (q.v.). Persons differ in susceptibility, blonds being especially sensitive. Erythema limited to the exposed areas has its onset within a few hours after exposure begins, the interval depending on susceptibility and dosage. Vesiculation is characteristic of severe exposure, and extreme cases are sometimes seen. If a large area is involved, in addition to pain, smarting, burning and swelling there may be severe constitutional symptoms, including weakness or collapse, fever, chills and even delirium. Secondary infection may complicate the condition. Maximum intensity is reached within 12 to 24 hours after exposure, and recession of signs and symptoms then begins. Peeling follows and is accompanied by itching. More or less temporary pigmentation ensues. Sometimes sudamina (q.v.) follows sunburn because of temporary hyperkeratotic obstruction of sweat ducts (Thomson: Lancet 1: 17[illegible] 1951).

Pigment production is probably not the main agency of acquired tolerance, for pigment in the basal layers of the epidermis does not protect the rete, which is the site of vesiculation when that occurs; thickening and increased opacity of the corneum which develop after exposure are the protection, according to Blum and Kirby-Smith (Sci 95: 703 194[illegible]).

Increased tolerance of sunshine follows administration of estrogenic hormones (Lancaster: South MJ 32: 313 1939), or [illegible] and cortisone suppresses to some extent the skin reaction to ultraviolet (Jarvinen: BMJ [illegible] 1951).

The welding arc provokes actinic injury, especially conjunctivitis (Rieke: J 122: 734 1943), but glasses, clear or tinted, protect the eyes from ultraviolet injury (Blum: WarM 4: 389 1943). Fluorescent light contains some ultraviolet energy and was reported as a cause of irritation by Bresler (J 140: 1344 1949) and James (ADS 44: 236 1941). Such artificial light perhaps may be harmful to patients with lupus erythematosus.

Chronic actinic injury is an occupational disorder of farmers, sailors and other outdoor workers (see Senile keratoses; also Light sensitivity dermatoses).

Physiologic Effects of Ultraviolet Light.—Antirachitic action takes place in the lowermost horn cells. Erythema results from action in the basal layer of the epidermis and the superficial portion of the corium. The basal epidermal cells are stimulated, and increased amounts of the products of their activity are set free; it is these substances which result in local hyperemia and which act also on distant parts of the body when absorbed and transported. Ultraviolet light produces maximum burning effect at a wave length of 2,96[illegible] A.U. The longest wave capable of burning is at 3,150 A.U. Too intense action kills the basal cells of the epidermis, so that ultraviolet irradiation is shock treatment, and its value depends on the individual's reaction to it. Care should be used to avoid overexposure. Not only may painful sunburn result, but more deep-seated injury may occur, as indicated by nervousness, apprehensiveness, and insomnia (Laurens: J 111: 2385 1938).

When parts of chromosomes were exposed to UV light by Uretz et al. (Sci 120: 197 1954), the movement of the chromosome from the centrosome region was inhibited only if the kinetochore was included in the irradiated part.

Treatment.—A soothing, cooling, protective mixture like calamine lotion is beneficial, or modified zinc oil may be prescribed.

℞	Phenol	0.3
	Menthol	0.06
	Zinc oxide ointment	
	Wool fat	15.0
	Limewater to saturation	
Sig	Soothing liniment.	

Sunburn is well alleviated by inunction with mineral oil and wrapping the parts with soft towels moistened with boric acid or aluminum acetate solution. The patient must be kept warm if extensive wet packs are necessary. Vesicles should be incised, and tetracycline ointment is valuable in combating or preventing infection. Later a bland greasy preparation is comforting.

A good preventive is [illegible] drams of zinc oxide in an ounce of Aquaphor. Phenyl salicylate (salol) 10% in liquid petrolatum, and stearates are also efficient in protecting the skin. A protective lotion may be prescribed, of skin-tinted red ferrous oxide 1.0, yellow ferrous oxide 1.3, titanium dioxide 15, bentonite 3, rose water to 100. Dark red vet. petrolatum is effectively opaque (Luckiesh et al.: J 130: 1 1946). Para-aminobenzoic

acid, 15% in Ruggles cream protects against rays of 2,000 to 3,100 A.U (Rothman and Henningsen JID 9: 307 1947) Pyribenzamine inhibits sunburn because the absorption curve of the chemical has a high extinction peak in the erythemogenous parts of the spectrum (Kline and Baer JID 10: 397 1948) A layer of zinc oxide paste generously powdered with talcum is effective. A fil containing 5% each of menthyl anthranilate and titanium dioxide is a good sun screen. Hemphill (NoWM 50: 4 4, 1951) combined phenyl salicylate 1.0 antipyrine 5.0 and sodium para aminobenzoate 5.0 in Almay emulsion base 100. Hydroquinone is unsuitable being both allergenic and toxic according to Draize (ADS 64: 585 1951) Para-amino benzoic acid was thought superior to its sodium salt by Fisher (ADS 68: 723, 1953) who gave the pharmaceutics of preparing a vanishing cream containing PABA 4.5, water 6.0 hydrophylic ointment 6.0 and base q to 30.0. Evaluation experiments of Ba ber (JID 23: 4 1954) indicated that the sun screening effect *of the tannic acid and PABA compounds were superior and that menthyl anthranilate was* inferior in effectiveness. Neo-A Fil (Texas Pharmacal Co.), containing 3% digalloyl trioleate in a vanishing cream base is commendable; it is said to block completely solar radiation from 2,000 and 3 150 A.U but it may cause contact photosensitization (p 147)

See Sharlit (ADS 32: 390, 1935) Strakosch (JID 5: 1 1942), Russell and Anderson (Lancet 2 247 1950), Bachem and F tus (AIPhysTh 20 49, 1939); Schwartz and Peck (Cosmetics and Dermatitis, Hoeber 1947 p. 144); Partington (ClinSci 13 425, 1954) vascular responses t UV not due to release of histami

X RAY AND RADIUM INJURIES OF THE SKIN

The influence of x rays and radium is necrobiotic (see Treatment x ray effects) Some kinds of cells are more susceptible than others to this effect, which is proportional to the quantity of x ray energy absorbed. Judicious use may be made of this phenomenon unfortunate results are radiation burns.



Fig 81.—Radiation trophy of kin and nails. (Dr C P G Wakeley)

Symptoms.—Gilchrist (BullJHH 8 17 46 1897) recognized the specific skin disease caused by x rays. Reactions vary in degree erythema, vesiculation, or even gangrene may result Reaction appears after from 2 to 10 days, the sooner when more severe In mild acute reactions, the redness, which is accompanied by tenderness, burning and itching disappears within two or three weeks, leaving temporary pigmentation such as follows sunburn. There may be periodic recrudescences of erythema which rapidly diminish in intensity but are observable for several weeks. In chronic cases which result from excessive employment of doses which if taken singly would not give rise to erythema the skin becomes thin, dry atrophic wrinkled, telangiectatic and pigmented Keratoses may develop and some of these may become carcinomatous. Nails become thinned, striated and brittle. In severe burns

marked dermatitis develops with vesiculation followed by more or less necrosis. Ulcers thus formed are covered with thick tough, adherent, brownish or grayish membranes and are exceedingly painful They heal slowly if at all Radium burns are similar but are smaller in all three dimensions.



Fig 32 —Roentgen dermatitis with chronic ulceration.





Fig 33 —X ray dermatitis of cheek, with consequent carcinoma. (Dr John Butler)
Fig 34.—Alopecia resulting from roentgenography with primitive equipment (Dr Frederick O Harris)

The most common cause of x ray burns is failure to insert filters when treatment is planned to include their use (Saunders and Montgomery J 110 23 1938) Mistaken diagnosis, inadequate records of previous radiotherapy improper calibration, faulty fluoroscopic technic unwise therapy in diseases for which x ray is only palliative, and stupid disrespect for or ignorance of, the harmful potentialities of exposure are other causes (Leddy and Rigos AmJR 45 696 1941 Garland J 129 419 1945 Curtis ClevClinQ 9 3 1942)

The hands are involved in a high percentage of cases of roentgen injury and a large proportion of the patients are doctors, dentists and x ray technicians (Mason AmSurg 17 1121 1951) Frequently repeated small exposures seem to promote the development of cancer more than intensive ex

posures. The treatment is likely to be of necessity excision. Fingertip burns from using x ray diffraction apparatus may simulate infections or thermal burns; interesting cases were recorded by Watrous et al (J 152 513 1953)

Shoe-fitting fluoroscopes entail significant hazards, and these devices should be decried (Hempelmann NEngJM 241 335 1949 Edit J 139 1004 1949) Their output is from 12 to 107 r per min with a mean of 38 r per min., according to Lewis and Caplan (CalifM 72 26 1950)



Fig. [illegible]—Multiple carcinomas and roentgen atrophy of gluteal region caused by x-ray therapy of pruritus ani.

Pathology—Early there is edema of the epidermal cells, followed by degeneration of nuclei. *Vascular endothelium is similarly affected. Severe doses* cause necrosis, hemorrhages and obliteration of small vessels. Fibrous tissue nuclei swell and fragment, and collagenous tissue takes a mucoid appearing stain. The epidermis becomes flat and atrophic and appendages are lost (Harvey EdinMJ 49 529 1942)

Chemical analyses of epidermal changes in the mouse produced by soft x rays showed calcium diminished by 50%, while epidermal lesions resulting from the application of methylcholanthrene contained 50% less calcium than normal (Toosy; CaRes 11: 361, 1951)

The scars of radiation burns show light blue fluorescence at the periphery in Wood's light, while scars from mechanical, chemical and electric burns are not fluorescent, according to DeMent (Sci 103: 631 1946)

See Carcinoma, etiology x ray; Erythema, symptomatic, following x-ray therapy

Treatment.—In severe cases, excision followed if necessary by grafts, may be necessary Pain is relieved at once. Aloe vera, a gelatinous material applied as a poultice and effective largely because of its physical properties, was reported on favorably by Loveman (ADS 36 838 1937) Tchou (ADS 47 249, 1943) Cole and Chen (ADS 47 250 1943) and Lushbaugh and Hale (Canc 6 690 1953) In mild roentgen dermatitis, astringent soothing lotions, such as aluminum acetate alleviate Boric acid ointment or Neobase with 0.5% phenol is a suitable bland protective tetracaine 0.5 to 1.0% may be added. Sellers (JMichSMS 41 59 1942) recommended Theelin in oil, 10 000 units per cubic centimeter locally Late cases may be helped by superficial desiccation (Cannon NYSJM 40 391 1940) or major surgical effort may be required (Bevan SClinNAm 1 935 1921 Ghormley and Fairchild Surg 7 737 1940) Chronic ulceration in postirradiation scars responded favorably to weekly infiltration with about 0.5 cc. of penicillin, 50 000 units per cubic centimeter into each 1 cc. of affected tissue, after preliminary infiltration with

1% procaine reported Lamb and Bover (JID 11 3 1948) Ulceration may be due to low grade infection Chlorophyll ointment received the approbation of Holmes and Mueller (AmJRoent 50 210 1943)



Fig 46.—Acute x-ray injury showing hydropic degeneration and karyorrhexis of epidermis. (Dr F D Weidman.)



Fig 47—Chronic x-ray dermatitis atrophy of epidermis, dilation of vessels, advanced degeneration of collagenous tissue absence of appendages. (Dr George M. MacKee, from McCarthy Histopathology of Skin Diseases, Mosby)

Corticotropin ameliorated the symptoms and prolonged the lives of mice which received 300 r total body irradiation and it appeared to help patients with radiation sickness due to therapeutic irradiation (Taber Radiol 57 702, 1951) Preliminary cortisone dosage reduced the reaction and damage produced in the skins of guinea pigs by large doses of x ray energy as compared with controls, reported Houghton et al. (BMJ 2 1313 1954)

Aurofac the residue of Aureomycin production is notably beneficial in radiation sickness, Mark Marks told me

Cathode Ray Injuries of the skin and eyes were reported on by Robbins et al (Radiol 46: 1 1946) The injuries resulted from a few second exposure to scattered electron from a 1,200 KV electrostatic generator There were three phases in the reactions, the last appearing four weeks after exposure The primary reaction resembled intense sunburn and the secondary reaction comprised edema and bleb formation. No lesion was deeper than the dermis although some lesions underwent ulceration. The reaction appeared sooner than severe roentgen ray injuries caused less pain, healed more rapidly and did not produce tanning though the late effect of both were similar

ATOMIC ENERGY INJURIES

The medical effects of the atomic bombing of Japan during World War II were reported by Keller (J 131 504 1946) Timmes (USNMB 48 219 1948) and others. In addition to mechanical effects, burns and suffocations due to conflagration, many casualties were caused by actinic flash and fewer by ionizing radiation. Actinic injuries were numerous and severe and were ill attended for the most part, to some extent because of the catastrophic proportions of the havoc inflicted Infection was usual and added its major contribution to the disastrous effects of burns, yet the keloidal sequelae were not too common, according to Warren (MilSurg 102 93 1948) Novy (ADS 61 379 1950) examining Hiroshima survivors 3 years afterward saw only ordinary scars of flash burns. Scars, keloids, alopecia and cataract from radiation were described by LeRoy (J 143 1143 1947)

In preparing to meet atomic attack burn casualties in the thousands must be expected and their care planned for (Evans J 143: 1143, 1050; 145: 134, 1951) Flash burns will constitute the majority of the casualties. Superficial burns are the ones that are painful, for deeper burns destroy nerve endings. The area immediately beneath the air burst of an atomic bomb is subjected to the combined effects of blast, gamma and neutron radiation and intense heat' Evans wrote The devastation here will be so great as to result in practically total loss of life (immediate or delayed) so medical attention must in the main be directed to the survivors outside the 1,500 yard zone, from 1,500 to 4,000 yards. Thermal injury in survivors outside the hypocenter zone will be of three types: the flash burn, contact burns from ignition (or heat transfer to skin) of clothing and deep burns from contact with flame encountered during entrapment in or escape from burning buildings. [Evans figures have to be revised to accord with refinements in the construction of atomic weapons.] The atomic flash burn differs from ordinary burns of civilian life only in that it results from exposure of the skin to a large amount of radiant energy (infrared, visible and ultraviolet) in a very short rather than a long period of time.

The principles of management of flash burns in no way differ from those for other thermal burns (q.v.) Acute radiation injury is discussed by Dunham et al. (J 147 50 1951) as it concerns atomic energy phenomena. It is to be distinguished from irradiation sickness, which results from therapeutic irradiation from surface radiation injury from exposure to radioactivity other than atomic explosion and from the selective deposition, such as in bone or thyroid, of radioactive substances inhaled or absorbed. The initial nuclear radiation from an atomic bomb explosion consists of gamma rays and neutrons emitted during the first one minute. The syndrome of acute radiation injury due to exposure of the whole body will affect especially those who are completely exposed, while various degrees of exposure will be experienced by those who are to various degrees shielded by the aggregate of the various amounts of matter (preferably several feet of earth and concrete) situated between the nuclear reaction and the individual. Casualties can be classed as uncomplicated radiation injuries and radiation injuries complicated by burns and wounds.

Three fairly distinct forms of uncomplicated acute radiation injury may be summarized (1) very severe cases (whole body exposure of 600 r or more) with malaise nausea and vomiting beginning within 2 hours, rapidly developing severe leukopenia, diarrhea and rising sustained fever during the next few days, and death in coma and delirium within two weeks, often showing purpura and epilation shortly before death; (2) *severe cases* (exposure of about 400 r) with nausea and vomiting occurring a few hours after exposure but not persisting more than 24 hours, lymphopenia on the second day a period of relative freedom from symptoms but with some malaise and fatigability persistent lymphopenia and fluctuating leukopenia but developing serious illness at any time up to the 20th day showing any or all of these symptoms epilation purpura, oropharyngeal ulceration, diarrhea, fever severe leukopenia, infection, sepsis, and death, which is the fate of about half such cases, especially those with untreated sepsis or with predominantly hemorrhagic symptoms and (3) *mild or moderate cases* (exposure of from



Fig. 88.—Flash burns. Darker portion of striped garment absorbed more heat and produced pattern. Photograph made 3 weeks after atomic bombing of Japan in 1945. (Armed Forces Institute of Pathology.)

Fig. 89.—Flash burns of uncovered skin. (Armed Forces Institute of Pathology.)



Fig. 90.—Flash burns. (Armed Forces Institute of Pathology.)

Fig. 91.—Keloidal scarring following flash burns, showing protection afforded by shoulder straps. (Armed Forces Institute of Pathology.)

200 to 400 r) with vomiting a few hours after exposure no definite symptoms except moderate lymphopenia during the next two weeks, and later some epilation, especially of the scalp malaise, sore throat petechiae diarrhea and weight loss. In general few who are farther than a mile from the hypocenter will experience severe radiation injury (Hiroshima experience) Early appearance of symptoms is indicative of severe injury See Bowers (J 145: 63, 1951)

If vomiting occurs on the day of the bombing and is followed by diarrhea, prostration and fever survival is improbable (Cronkite: Radiol 56: 661 1951) If vomiting occurs on the day of bombing and is followed by an asymptomatic period of from 1 to 3 weeks before purpura mucosal ulceration and epilation appear survival is possible If there is no vomiting within 24 hours survival is probable unless complications intervene such as thermal burns mechanical injuries or epidemics.

Treatment from the beginning should be directed at minimizing the effects of the tendency to hemorrhage and inability of the individual to combat infection. The patient is sensitive to physical activity and should not be transported long distances. Replacement of fluids, restoration of electrolyte balance and sedation are the first measures. Later come control of infection and treatment for hemorrhage and anemia. Those patients who are going to die do so despite treatment. Those who can be salvaged belong to the group who may be considered to be suffering from a self limited illness which they are to be tided over Antibiotics and transfusions are the mainstays of these efforts. Later in dealing with the postirradiation syndrome nutrition becomes an important problem, along with the control of communicable disease (Allen et al.: J 145 704 1951)

Casualty control and organization of physicians in case of atomic war are discussed by Bauer (MilSurg 103: 65 1948) Jacobson et al. (J 130 128 1949); Behrens (Atomic Medicine Nelson 1949 pp. 416) The organization of Civilian Defense and the training of large numbers of civilian personnel do not concern us here.

Radiation Accidents that resulted from temporarily uncontrolled fission reaction were reported on by Hempelmann et al. (AnnIntM 36 279 1952) Beta ray burns of the hands in four persons engaged in handling radioactive materials were described by Knowlton et al. (J 141: 239 1949) Erythema and tingling began in the first day with edema for two or three days longer and were followed by a latent period of from 3 to 5 days, then by secondary erythema and vesiculation, which healed in three weeks, leaving atrophy Biologically speaking, x rays, gamma rays, alpha and beta particles and neutrons differ for the most part only in the distribution and the magnitude of the destruction produced wrote Ingram (Sci 111: 103, 1950) The seriousness of the hazard encountered in work involving any type of radioactive isotope is dependent in part on the half life of the isotope under consideration. Other factors being equal the longer the half life, the greater the hazard. Ingram discussed the safety measures requisite to working with these substances.

See Liebow et al. (AmJPath 25 853, 1949), pathology of atomic casualties Haddow et al. (Biological Hazards of Atomic Energy Oxford Univ Press, 1952) Shirabe (MilSurg 113 251 1953), atomic bomb casualties in Nagasaki Behrens et al. (Atomic Medicine, Williams and Wilkins, edit. 2, 1953) National Research Council of Japan (Medical Report on Atomic Bomb Effects, Tokyo, 1953) Lenihan (Atomic Energy and Its Applications, Pitman, 1954) physics, reactors, weapons, hazards, medical and other applications of atomic products Byrnes et al (J 157 21 1955) choroid and retinal burns may result from looking at detonation from a distance of several miles.

DERMATOSES DUE TO CHEMICAL AGENTS

DERMATITIS FROM DEFATTING

Solvents and surface active agents, including soaps abstract oil from the skin. Frequent subjection of the integument to them results in damage which is chemical in origin but is not a sensitivity phenomenon. Individuals vary in their susceptibility to this abnutzung dermatitis, the red haired and xerotic patient being especially vulnerable Disease is more likely to occur during winter months when artificially heated air is of low humidity and sebaceous secretion is at its seasonal minimum.

Like dermatitis caused by primary irritants defatting may damage any skin. The hands are the usual site and occupation such as that of the housewife is a predisposing etiologic factor Soap takes out oil more effectively when used with hot water and the girl with chapped hands will accept good advice when one explains, You can t wash dishes free from grease with cold water

Manifestations of dermatitis from defatting include dryness and inflexibility of the skin, especially over the knuckles and hyperkeratosis, with some scaling and perhaps fissuring Treatment promptly relieves if contact with the defatting agent is sufficiently reduced and the skin is lubricated with hydrous wool fat or an equivalent. See Campbell (IndustHyg 7 5 1947)

CONTACT DERMATITIS

Symptoms.—Dermatitis venenata (contact dermatitis, eczematous or allergic dermatitis) is dermatitis due to cutaneous reaction to chemical substances when they have touched the skin. All degrees of inflammation from simple hyperemia to gangrene may be encountered Most cases are at first itchy then erythematous, and are limited to the regions touched by the irritant Later they become papular and vesicular and pustular if secondarily infected. The lesion may spread beyond the borders of the zone of original contact and widespreading manifestations may appear scattered over the body depending on conveyance via fingers or clothing and on the degree of cutaneous reactivity to the contactant. See White (Dermatitis Venenata An Account of the Action of External Irritants Upon the Skin Boston 1887)

Included within the meaning of dermatitis venenata are all inflammations of the skin provoked by contact whether the agent is a primary irritant which acts with substantially equal effect upon all skins (nitric acid lye) or is a sensitizer which acts with various intensities on different skins because of hypersensitivity Some chemicals are both primary irritants and sensitizers (ADS 45 1167 1942)

The argument that poisoning and allergic reactivity are different only in a quantitative way insofar as contact dermatitis is concerned was discussed by Anderson (IndustM 12 584, 1943) in a thought provoking manner

The eruption which results from a single contact with the offending substance is self limited It disappears spontaneously within a few days or weeks. Repetitions of contact are often the case however The response of the sensitive skin may become progressively more intense with spread of reaction far beyond the original site

The clinical picture and the history that the patient gives intimately depend on the time intervals involved daily association with a deleterious agent evokes continuous and chronic disease while occasional flares result from and denote corresponding occasional contacts. Thus investigation of

etiology in a given case requires intelligent questioning of the patient for periods of freedom from disease are as significant as periods of activity A period of freedom from disease denotes the fact that whatever the patient did touch during that time was not poisonous to him. The time interval from the moment of contact until dermal injury is apparent may be a matter of moments with primary irritants, but ranges from 4 to as much as 72 hours with allergens. Thus when an allergic reaction first starts, one is keenly interested in what was touched perhaps 12 hours previously







Fig. 92—Ulcers due to droplets of chromic acid solution used in chrome plating.
Fig. 93—Wristwatch strap (leather) dermatitis (Dr F Ronchese.)
Fig. 94—Iodoform dermatitis (Dr J W Perkins)



Fig. 95—Onychia caused by sugar in a bakery employee (Dr Clyde L Cummer)

The first manifestation of the allergic reaction is usually itching followed by redness A patient can be taught to be alert to these facts, and many a patient, instructed by a dermatologist solves his own problem of what contact damages him. Teaching the patient to profit from a flare is not ordinarily difficult to do Certainly flares, so interpreted, supply valuable clues as to what to suspect and what to utilize for patch testing (p 128)

Continuous or frequently repeated exposure results in disease which reaches maximum intensity and either remains unchanging or spreads in extent. Dermatitis may become universal, a form of exfoliative dermatitis (q v) and this may take place suddenly suggesting that degree of sensitivity may increase abruptly

Lesions of contact dermatitis are notably itchy as a rule more so than their appearance suggests. The hands, forearms and face are the sites of



Fig. 96.—Dermatitis from shoe strap.

Fig 97—Carved wooden ornaments of a necklace provoked dermatitis where they touched the skin.



Fig. 98.—Eczematous reaction t scalp lotion (Dr J Lamar Calloway)

Fig. 99.—Dermatitis from sunburn preventative. (Dr J Lamar Calloway)

predilection, although no region is exempt. The variations of area and of severity of involvement are not limited.

Such morphologic and out-of-date names as erythematous eczema vesicular eczema chronic eczema and fissured eczema are not sufficient to identify the disease and to satisfy the need for interpretation. Eczema I define as dermatitis of undetermined cause Dermatitis always has a cause though this may be difficult to identify Dermatitis due to a dye paraphenylendiamine for example might at different times in one person manifest a variety of morphologic forms, ranging from bullous inflammation to lichenification Merely to name it acute erythematous eczema at one time and chronic lichenified eczema at another would imply failure to comprehend the phenomena manifested.

If sharp distinction is lacking between chemical traumatic dermatitis and allergic contact dermatitis, except number frequency and intensity of contacts, it is equally lacking between contact dermatitis and the hyperergic reaction to the products of parasites reaching the skin from upon it within it or via the vascular system from distant foci, dermal or elsewhere When one judges from the hands alone one cannot differentiate between pompholyx



Fig. 100.—Contact dermatitis of eyelids, i this instance due to nail lacquer (Dr Wm. L. Dobes.)

Fig. 101.—Preauricular p tch of contact dermatitis due to nail lacquer (Dr Wm. L. Dobes.)

due to sensitivity to chemicals of known composition, and pompholyx caused by dermatomycosis of the feet. Arsenical dermatitis due to intravenous medication looks like contact dermatitis and perhaps is not fundamentally different from it. If one identified all cases of dermatitis venenata dermatomycosis, dermatophytid, bacterial dermatitis, dermatitis dependent on focal infection (bacterids) on food allergy or on nutritional deficiency and combinations of these, then few cases of eczema would remain undiagnosed.

Irritation provoked by medicinal chemicals, such as mercury is dermatitis venenata of medicinal origin. Dermatitis venenata includes the effects of both primary irritants and sensitizers. I recognize that the etiologic emphasis in the one class is to be placed on chemical trauma and in the other class on allergic reaction. There seems, however, to be no hard and fast line of distinction to be drawn between the two One must interpret the hyperergic response as the physiologic response to some sensitizing irritants, just as a purulent inflammation is to be expected as the physiologic response to *Staphylococcus aureus*

Eyelids are tender tissue readily capable of becoming swollen and itchy and are often involved in contact dermatitis. Flexural folds (neck, antecubital popliteal) and the delicate skin of the genital region are commonly attacked. These regions are probably often sites of the mediate contact, noxae

being carried by the fingers. Dermatitis caused by shoe dye, garters or stockings may provoke eyelid inflammation. Repeated attacks of swelling and itching of the eyelids, with redness, infiltration and loss of flexibility are practically always due to dermatitis venenata. While drops containing

MEN WOMEN BOTH SEXES

Fig 102.—Men. Cosmetics include ...

atropine may be the cause in a given case of itching lids, one must usually seek noxae through the whole gamut of air borne, water borne, medicinally or cosmetically applied, occupational, seasonal or other contacts with any part of the entire body surface. Fungus allergy may provoke an exactly

similar response For the most part eczematous reactions do not differ with different allergens there are exceptions (see Nickel and Chromium dermatitis)

HARDENING, the phenomenon of development by the exposed individual of ability to withstand contacts at one time injurious to him is commonplace especially in industry The workman stays on the job despite his dermatitis, unless the injury is extreme and he has perhaps 9 chances out of 10 of becoming hardened, as Schwartz (MichSMSJ 39 179 1940) demonstrated See Peck et al. (IndustM 14 214 1945) The private practitioner is likely to see only the patient who for unknown reasons failed to harden.

Pathology—Studies of especial excellence are those of Miller (ADS 56 678 1947) and Polak and Mom (JID 13 125 1949) The earliest change in allergic eczematous dermatitis is primary microscopic vesiculation appearing in the stratum mucosum, epidermatis, constituting cytoplasmic alteration and lysis of a few Malpighian cells (vésiculette primordiale of Civatte) preceding spongiosis. Vesicles are formed by confluence of these tiny lesions along with the canals resulting from intense spongiosis. The phenomenon was interpreted as perhaps toxic rather than allergic by Miescher (Dermatologica 104 216 1952) The dermal inflammatory process is nonspecific appears later and seems to be secondary to the epidermal change In some cases the dermis is the shock tissue and the epidermis secondarily becomes acanthotic, hyperkeratotic and variable in thickness. Leukocytic infiltrates in allergic disease contain a relatively high proportion of eosinophils.

Epidermal and dermal sensiti ity not rarely coexist (Templeton: J 1?7: 003 1945) Epstein (AnnAllergy 4: 429 1946) coined the name dermitis for contact dermatitis wherein epidermal hypersensitivity was not the significant feature but intracutaneous tests of the dela ed t berculin type were positive He observed such cases with sensiti ity to Rivanol, nickel and penicillin. Epstein (AnnAllergy 10: 633, 1952) offered an interesting hypothesis regarding the immunologic nature of contact dermatitis: The antigen is to be thought of as a complex of a simple chemical hapten joined with a prot in to form a protigen' and a given hapten may so join with any of several different proteins so a to give rise to various protigens, thus accounti g for various clinical mani festations of disease producible by one chemical substance Conceivably a hapten may not form a conjugate nd yet may alt r body-own proteins so that they become antigenic with resultant autosensitization' (q.v.)

The derml may be the shock organ i contact dermatitis, as wa shown by Epstein (TransADA, 1953) who described both immediate urticarial and delayed eczematous and tuberculo d reaction to patch tests with nickel and chromium in certain patients. Thu his pat h test sometimes elicited dermal reaction without epidermal and, furthermore he found individual who ha l contact dermat tis but evi ced no reaction on patch testing

Etiology—Review matter on allergy The problems of altered reactivity are gradually becoming clarified It seems safe to make these generalizations (1) all human beings can develop hyperreactivity to some things under some circumstances (2) the degree of reactivity in a given person varies with the manner of contact and quantities, durations and time intervals involved (3) clinical manifestations depend on (a) the reactive tissue whether dermal epidermal or both, (b) degree of reactivity (c) location, duration, intensity and frequency of contact and (d) bacterial medicinal, and other complications superimposed. Little is known about why sensitivity appears. Its onset may be sudden after years of previously innocuous contact. The farmer with ragweed dermatitis is an adult who met the allergen for years without having had symptoms. Burns, abrasions, moisture heat tinea, staphylococcic dermatitis and hyperhidrosis render a person more vulnerable. Some people are prone to develop sensitivities and other are not

Of some 230 cases seen in private practice drugs caused 71 weeds 31 clothing 21 cosmetics 17 soaps 11 physical agents 5, nickel 4 and matches 2, in the experience of Wilson (NebrSMJ 22 310 1937) Osborne and Hallett (NYSJM 42 1929 1942) listed numerous common irritants, and the causes in 250 cases were reported by Howell (ADS 53 265 1946)

While chemical sensitization may succeed dermatomycosis—a matter of significance in industrial dermatology—it is likewise common for nonparasitic

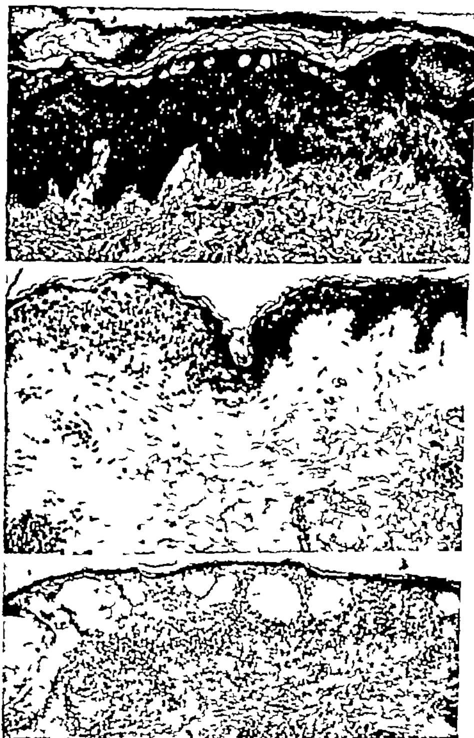


Fig. 103.—Pathology of dermatitis venenata. *Top*, Edematous degeneration of superficial epidermal cells, poison ivy. *Middle*, Slight epidermal edema and mild inflammation, patch test with mercurial antiseptic. *Bottom*, Vesiculation and inflammation, patch test with turpentine. (Miller: AD&S 56: 678, 1947.)

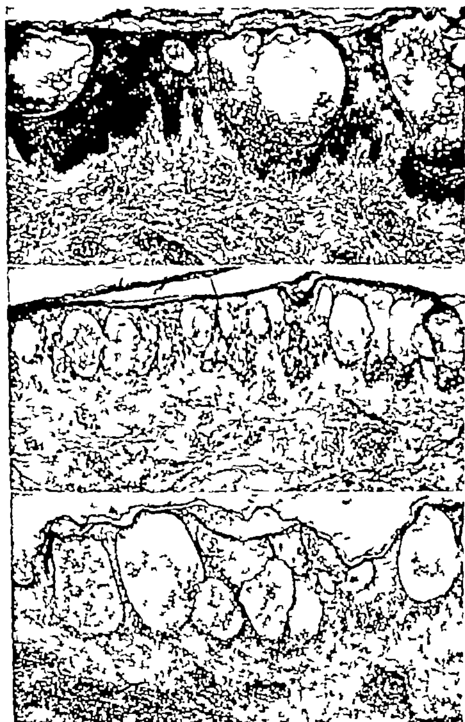


Fig 104.—Pathology of dermatitis venenata. *Top* Intense vesicula epidermal reaction to hair dye. *Middle* Vesiculation in eczematous dermatitis. *Bottom* Intense vesiculation, poison ivy (Miller ADS 56 678, 1947)

contact dermatitis to become complicated with *parasitism dermatitis of the* neck becomes complicated by seborrheic dermatitis from the scalp, or ivy dermatitis by micrococci from the pharynx or dermatitis of the hands by monilid from inconspicuous vulvovaginitis, or perianal and pedal epidermophytosis by medicinal dermatitis. It is such combinations which comprise the confusing cases once called eczema See *Chronic dermatitis of undetermined cause*

EXPERIMENTALLY it is possible that sensitization to some simple chemical substances may be induced by injection of conjugates of the simple substance with certain proteins such as red blood cell stroma (Landsteiner and Chase JExpM 66 337 1937 73 431 1941) Conjugation with staphylococcus toxin may render autogenous proteins such as rabbit skin antigenic to the homologous or even the same animal (Hecht et al JExpM 78 59 1943)

Allergic reactivity to a simple aliphatic acid acetic anhydride was observed by Weil and Rogers (JID 17 227 1951) Sulzberger and Baer (JID 1 45 1938) studied dermatitis produced experimentally by related, simple chemicals of known composition (chlornitrobenzenes) and *showed that the* ability of each to produce contact dermatitis in human beings paralleled the ability to produce skin sensitization in guinea pigs, and that this property seemed related to the lability of the Cl and NO_2 groups. Wise and Sulzberger (AmM 28 4 16 1933) studying the reaction to butesin picrate described 3 time periods, those of (1) refractoriness, which may persist for months despite contact (2) incubation of 9 or 10 days and (3) development of reaction 16 to 48 hours after the contact after allergy has, during the refractory period come into existence Subsequent contacts, after sensitization has been accomplished take place promptly skipping the refractory period

The nature of antibodies responsible for contactant allergy has not as yet been determined they must be local have not been isolated and are not passively transferable (Leider and Baer JID 10 425 1948) When sensitivity has developed to one chemical, reactivity to primary irritants of other chemical varieties is not influenced (Haeberlin JID 10 27 1948) The studies of Rokstad (ActaD-V 26 1 1946 suppl. 15) using turpentine derivatives were interesting the toxic *primary irritant* effect was of short latent period 24 hours or so and erythema swelling even pustulation developed depending on intensity of exposure the purely eczematous effect in sensitized persons might appear within a few hours or might be delayed even 3 or 4 days and the most intense exposure flared earliest. If during the sensitizing exposure the skin is necrotic the necrosis appears to protect against the development of eczematous reaction

Eczematous sensitization is highly specific (Rostenberg and Kanof JID 6 201 1945) yet cross sensitizations and group sensitivities do occur and have been studied extensively in the search for elucidation of the obscure nature of sensitization phenomena

Sensitization from the initial substance *may spread so as to embrace other* substances of related or nonrelated chemical nature and a person who has contact dermatitis is twice as susceptible to other materials as a person not so affected (Sulzberger and Rostenberg JImm 36 17 1939) Group specificity in epidermal allergy follows a pattern similar to that of serologic reactions, write Rothman et al. (JID 6 191 1945) Patients of Leifer and Steiner (JID 17 233 1951) sensitive to Vioform and Diodoquin were also sensitive to Quinolor and Sterosan manifesting a group sensitivity to halogenated hydroxyquinolines and they were furthermore sensitive to three carboxylated pyridines

Cross sensitization to the para group was studied by Sidi and Dobkevitch Morrill (*JID 16 299 1951*) *Serious accidents can* be caused not only by an agent which has sensitized the patient but also by chemically related substances. The sulfonamide and local anesthetic groups are the most hazardous.

Parallelism between the abilities to excite mitosis and to evoke sensitivity was noted by Bujard et al. (Acta Allergica 6 161, 1953) Nonsensitizing primary irritants induced necrosis but did not stimulate mitosis, it was observed in testing the effects of several benzine derivatives.

The route of spread of sensitization continues to be a baffling problem (Rostenberg ADS 56 222, 1947) If skin is circumvallated by incision and the island so produced then sensitized by dinitrochlorobenzol the island may be sensitized while the remainder of the skin remains nonallergenic. In controls, sensitization of a spot produces sensitization of the whole So skin contact sensitization seemed to spread via the cells not by way of the blood (Schreiber and Müller DWchn 107 1393 1938)

Eczematizing chemicals were applied to circumscribed areas of skin which were circumvallated to form islands after 6 12 and 24 hours by Rostenberg (JID 8 345 1947) Despite circumvallation sensitization became generalized in all instances, suggesting that the simple allergen formed an antigenic conjugate at the site and this was absorbed via lymphatic or other routes.

Experimental sensitization of the skin to dinitrochlorobenzene was studied by Haxthausen (ActaDV 20 257 1939 23 438 1943) who reported his transplantation of sensitized skin from one identical twin to another replacing the donor area with nonsensitized skin from the normal twin. Three weeks after transplantation previously normal skin growing in the sensitized twin had become sensitive and the previously sensitized skin now attached to the normal twin was not reactive The capacity to react did not move with the full thickness transplant but the presence or absence of this capacity was determined evidently by influences outside the transplant

The white blood cells were thought to transmit dinitrochlorobenzene allergy in guinea pigs by Haxthausen (abs BJD 64 313 1952) but Baer et al (JID 18 53 19 217 1952) were not able to achieve passive transfer of contactant allergy in man by means of white blood cells obtained from eczematous donors. Experiments of Curtis (ADS 65 149 1952) with protein extracts from the skin of allergic donors likewise failed to demonstrate antibodies. Heparin appears to inhibit the development of allergic dermatitis according to Haxthausen (JID 19 203 1952 21 237 1953) who reported inconclusive results of intradermal transfers of living lymphocytes from sensitive persons in an effort to transfer their reactivity

Human skin explants were exposed to dinitrochlorobenzene poison ivy antigen and old tuberculin by Everett et al. (JID 18 193 1952) No difference in capacity for growth was exhibited by explants from sensitive and nonsensitive donors.

Experimental sensitization of various creatures other than man was reviewed by Rostenberg and Haeberlin (JID 15 233 1950) Chickens, ferrets monkeys and pigs have developed sensitizations. The evidence is questionable in the case of dogs, rabbits and white mice

Testing the effect of nervous exhaustion on susceptibility Guy (ADS 66 1 1952) subjected guinea pigs to repetitious electric shocks so as to cause them to lose appetite sleep and weight The animals then showed increased sensitivity to contactants.

Diagnosis.—That dermatitis is due to external irritant chemicals can generally be inferred promptly from the clinical examination I know of no easy way to learn contact dermatitis, saving long experience One must possess familiarity with the irritating potentialities of all the things which may touch various parts of the body in individuals of both sexes and any age. This knowledge is gained gradually as one reads about thinks about, and sees dermatologic patients. If a physician knows a good deal about contact dermatitis, he knows the major portion of practical dermatology for dermatitis venenata and its complications constitute a high proportion of dermatologic work.

In general the onset is acute and the lesions itch. The edges of lesions are likely to be fading rather than sharp because an irritant usually touches

the skin in greater concentration at a central site and in lower concentration peripherally. Pus is not present until secondary infection occurs. When the complaint of itching seems out of proportion with the amount of skin disease seen, contactants are probably at fault.

The experienced dermatologist knowing all the other things that might be wrong with the skin will diagnose contact dermatitis by exclusion—a rash that isn't something else is contact. To control contactants is essential in the management of almost any dermatitis for an element of contactant trouble is present in almost every case of dermatitis the physician handles. If it was not there to start with his medicines may provoke it.

Location of onset is the first clue to the nature of the noxious agent. The manner of reaching the skin obviously influences the location. Allergens *reaching the skin as air borne dust settle in greatest concentration on ex*posed parts, moist parts, and where clothing constricts. Itching eyelids are almost invariably due to contact dermatitis (Hazen ADS 49 253 1944; Ratner J 103 180 1934)

The longer the dermatitis has endured the more difficult it is, as a rule, to discover the allergen. Soap and medication are the commonest causes of contact dermatitis with a long continuous history. Flares give clues: contact must have been made within a few hours before the flare. The patient's understanding and cooperation are of primary importance in the search. In the usual case it is imperative for the physician to give the considerable time necessary for the patient's enlightenment (Sulzberger and Rostenberg J Allergy 6 448 1935)

Identification of the cause can be a complex and tedious business. It is *easiest in persons of good intelligence some of whom suffer contact dermatitis,* recognize the cause, cure themselves and never visit a doctor. The history helps one decide what substances to do patch tests with, and skin tests (q v) may be used advantageously although they often are largely a waste of time and energy (Sutton ADS 59 36 1949)

Diagnosis is proved by cure of the disease when irritants are avoided and identification of the causative irritant by positive reaction to contact with it.

Good references to study with the object of learning diagnosis include Sulzberger and Kerr (J Allergy 4 326 1933); Odland (NoWM 34: 9 1935); Fasal and Cornbleet (J 105 1062 1935); Wilson (NebrSMJ 22: 310 1937); Sutton (JMoSMA 44 451 1947). The patterns of contact with various things touched by the hands were carefully investigated by Waldbott and Shea (ADS 57 975, 1948; see Waldbott: Contact Dermatitis, Thomas, 1953). In dermatitis caused by shoes (Niles: J 110 363, 1938) vesicular eruption appeared on the feet when the offending shoes were worn and disappeared when they were not. Dermatomycosis was ruled out by the relationship of flare to the wearing of the shoes, by positive patch tests, by absence of demonstrable fungi, by severity of the itching which seemed disproportionate to the visible dermatitis, by freedom of interspaces from involvement, by predilection for the dorsum of the foot and by limitation of dermatitis to those areas of skin which were in contact with the shoes.

SKIN TESTS are immunologic procedures designed to ascertain the skin's capacity to react. They can be so standardized as to show whether cutaneous tissues have acquired some alteration in their capacity to react to certain agents. They are never the sole diagnostic method, and positive reaction is never proof of causal role while negative reaction never completely exonerates an agent, wrote Sulzberger and Baer (YBD 1943 p 7 1944 p 7). Performance, interpretation and exhaustive tabulations (diseases, concentrations and precautions) of skin testing are given in the 1943 reference.

Agents and their concentrations suitable for patch testing were listed by Rostenberg and Sulzberger (JID 2 93 1939)

Tests for sensitivity are of the contact, scratch and intracutaneous types. The intracutaneous test requires the least of the irritant material to cause re susceptibility to external irritants. These tests serve to reproduce a disease in miniature under controlled conditions. Passively transferable elements occur

in the blood serum of idiosyncratic individuals (Prausnitz and Küstner Zentralbl f Bakt 86 160 1921) In some instances, allergens affecting the skin are absorbed through the colon or via the respiratory route. In general, allergens that damage the epidermis are fat-soluble and produce vesiculation, while those to which the dermis reacts are water-soluble and evoke wheals. Contact tests (patch tests) are used to determine contactant irritants while scratch and intracutaneous tests are aimed at reaching the mesodermal issues with the allergen Passively transferable Prausnitz Küstner antibodies are likely to be present when the mesoderm is reactive and are absent when the epidermis is the shock tissue

Quantitative patch testing technic was designed by Dunn et al (JID 6 323, 1945)

Patch tests were carefully evaluated by Warren (SouthMJ 36 425 1953) and untoward results of such tests were studied by Epstein (JID 5 55 1942) Downing (ADS 44 63 1941) and Swineford and Radford (SouthMJ 41 667 1948) They are capable of initiating previously nonexistent allergy

Faults of patch tests include the fact that they do not reproduce physical properties (Siegel and Meltzer ADS 57 660 1948) A patient might tolerate the use of a soap three times a day and suffer damage using the same soap twenty times a day patch testing could not reveal this. Nor would patch testing incriminate wool trousers which in stationary contact with the skin did no harm but which through friction induced by walking scraped the legs raw Fallacies of patch tests and their deficiencies in diagnosis were discussed by Downing (NEngJM 219 698 1938) A case in which an industrial commissioner required a patch test with a notorious sensitizer resulting in severe disability and much medicolegal complexity was reported by Downing (ADS 44 63 1941) See Edit (J 156 500 1954) For the [patch] test to be highly effective it must be followed by a usage trial Of major importance is the fact that the patch test is continually subject to change and refinements and that absolute reliance upon its results in all cases of contact-type dermatitis is not justifiable (Council on Industrial Health Rpt J 156 497 1954)

The chief value of patch tests is corroborative wrote Rostenberg and Sulzberger (ADS 35 433 1937) when they are applied with skill and discernment as to what to suspect Practical application in occupational disease along with warning that unnecessary or unwise testing may cause severe reaction was discussed by Downing (ADS 48 514 1943)

When patch tests are repeated weekly in standard concentrations upon known reactors, the results are not always identical but are fairly consistent and the repetition of patch tests does not reduce sensitivity (Witten and Shair AnnAllergy 7 32, 1949) Strong concentrations of potential sensitizers used for patch testing may indeed induce sensitization which did not previously exist (Bechet NYSJM 39 829 1939)

PROPHETIC PATCH TESTING was designed by Schwartz and Peck (PHRpts 59 1 1944) to indicate the possible sensitizing effect of a new chemical substance intended for commercial applications such as would place it in contact with the skins of many people The substance must be tested upon at least 200 individuals who must be retested later to determine whether the initial test induced the development of sensitivity If even two or three individuals out of 200 subjected to prophetic testing showed intolerance the substance would be hazardous indeed if introduced widely among the population. Statistical validity of such testing was investigated by Henderson and Riley and by Knudsen (JID 6 227 231 1945) Their mathematical analyses indicated the number of reactors among groups of various sizes necessary to yield data of statistical significance See Schwartz et al (Occupational Diseases of the Skin, Lea and Febiger 1947 pp 59 306) Cox and Dehne (ADS 61 611 1950)

One may evaluate the capacity of a chemical to sensitize by performing repeated tests upon the same subjects, testing daily for 5 days, waiting 7 days, and then retesting (Brunner and Smiljanic ADS 66 703 1952)

Controlled use tests were preferred by Traub et al. (ADS 69 399 1954); in combination with prophetic patch testing the procedures predict the likely incidence of dermal reactions including the effects of prolonged contact

Excitant Causes of Dermatitis Venenata.—The list is almost interminable (Weber ADS 35 129 1937) Frequent chemical causes are strong acids and alkalies turpentine nail lacquer rubber cleansing agents, occupational hazards, incompletely polymerized plastics, medicines, wood tars, cosmetics, fabric finish, mercurial compounds and formalin. The concentration of the irritant is an important consideration (Rostenberg and Sulzberger JID 2 93 1939) Mucosa as well as skin, may be the site of contact inflammation which does not differ from contact dermatitis. Cheilitis and stomatitis, and dermatitis of the face or even of the hands may be caused by tooth paste mouthwash prostheses and other things.

ANIMAL SUBSTANCES occasionally incite dermatitis venenata although when fur is the cause the allergen is usually dye sometimes insect repellent

Among irritant items may be mentioned the resinous substance of beehives (Umansky DWehs 48 177 1934) the carpet beetle (Cormia and Lewis NYRJM 48 2037 1948); fishermen s Dogger Bank itch from the sea chervil (Bonnevie abs YBD 1948 p 168); coral (Preston BMJ 1 645 1950); swine itch in packing house employees (US Dept Agric Bureau Anim. Ind. Mar 1931) butcher s dermatitis from handling freshly killed carcasses (Schwartz JIndustHyg 13 233, 1931) See also Caterpillar Dermatitis and Occupational dermatitis in food handlers.

CLOTHING DERMATITIS is at first located at the actual site of usual contact. The noxious agent is usually a resinous fabric finish (Schwartz et al. J 115 906 1940) When nylon hose first became popular itching of the dorsa of the feet was often observed to have been caused by them. Faint redness with severe itching soon appeared on the legs and thighs, later spreading to hands and forearms due to contact during laundering which women usually do for themselves, and to the eyelids, later becoming universal

An abietic acid ester gum was the irritant in cotton underwear reported by Kell (ADS 47 242, 1943) Dermatitis from men s shorts, provocative of extreme discomfort and swelling of the genitals, was commonplace in 1942 (Costello and Ryan ADS 46 264 1942 and others) Many synthetic resins are potent sensitizers to be met not only in garments, but in glue plastics, etc and the dermatitis they cause while extremely pruritic may persist for weeks after contact has ceased (Schwartz JID 4 459 1941) Clothing dermatitis was excellently reviewed by Schwartz and Peck (J 128 1209 1945) Dyes, mordants, impregnations and the textile itself may be irritant as well as the finish. In shoes, the chlorophenol antimildew glue dye polish chrome or formol tanning agent or other component may be the specific irritant (Shaw ADS 49 191 1944) The fungicide was at fault in the case of Gaul and Underwood (IndianaSMAJ 42 22, 1949)

When a garment is suspected of being the cause the patient is instructed to wear nothing but clothing which was already 6 months old at the time his dermatitis began Such clothing previously worn and found harmless, may be trusted unless subsequently it was exposed to chemical contamination. It is probable that an injurious agent would be removed if the garment were subjected to repeated cleansing with carbon tetrachloride followed by soap and water and thorough rinsing Boiling alone will not remove it Soap starch, bleach bluing laundry antiseptics or substances from cleaning fluid may remain in a fabric rendering it irritant even though it may not have been irritating at the time of purchase Garment dermatitis is a serious matter of significance to the public health One wishes hypoallergenic garments could be purchased Recommendations regarding nonallergic bedclothes were given in QMN (J 142 1330 1950)

Fabric finish can be removed by 2 soakings in carbon tetrachloride followed by soap Schwartz told me

Paraphenylene diamine much purer than it used to be is seldom a cause of fur or hair dye dermatitis, and the requirement of prevue open patch test

ing, before its use on the hair discloses the susceptible individuals (Schwartz SouthMJ 46 769 1953)

See also dhobi mark dermatitis (p. 149) and glass wool and Fiberglas (p. 136). See Epstein (ADS 41: 1046 1940) clothing dye cases, contact dermatitis, photosensitization, hidradenitis, lichen chronicus, urticaria; Dobkevitch and Baer (JID 9 203 1947) azodyes in nylon stockings and cross-sensitivities Scott et al. (JPed 28 712, 1946) aniline laundry marking of nursery textiles caused cyanotic dye poisoning responsive to treatment with methylene blue; Anderson (ADS 61: 111, 1950), nylon hair net as vinyl rash on face Carpenter and Danner (USNMBull 43 754 1944), irritation from Navy blue uniform Davies and Barber (BJD 56 33, 1944) textile dermatitis in military personnel, Cox (BJD 54 22, 1942) chemicals in fabrics, Fleming (JID 10 281 1948) the array of hazard of dyes and fabric finishes, many of which are strong sensitizers, and it should be tested before exposure of the public to them; Mauersberger (Matthews Textile Fibers, Their Physical, Microscopic and Chemical Properties Wiley ed. 6, 1954), Hollander (AD 71 735, 1955) irritation by silvery metallic strands in woolen garment, Harris (Handbook of Textile Fibers, Harris Research Lab., Washington, D.C., 1954) physical and chemical data on textiles.

CLOTHING — DIAPER DERMATITIS is a name for any rash of a baby's nether parts. Diapers may retain enough detergent to irritate after home laundering; those done by diaper washing companies are nonirritating unless they have been treated with an antiseptic such as phenyl mercuric acetate (Dobes J 128 281 1945) Friction baby oil medicines soap wool, fabric finish of waterproof panties the mother's nail lacquer monilia, bacteria and *Acarus scabiei* often cause dermatitis of buttocks and thighs of babies.

"Napkin rash" has been attributed to ammoniacal decomposition of urine and boric acid powder and boric acid rinses of diapers may be tried. Since the diagnosis of "napkin rash" is about as explicit as that of "athlete's foot" critical evaluation should be made of such possible causes as soap baby oil antiseptic diaper rinses and other contactants, or scabies, infectious impetiginoid disease or moniliasis, or pityriasis rosea See Gordon (BMJ 1 383 1940) Forman (Pract 146 238 1941)

CLOTHING—SHOES AND LEATHER GOODS are often a source of trouble Tanning methods and leather chemistry are given by McLaughlin and Theis (The Chemistry of Leather Manufacture Reinhold 1945) Gaul and Underwood (ADS 60 649 1949) listed the primary irritants and sensitizers used in the fabrication of footgear dyes, tanning chemicals (Formol chrome) felt adhesives, rubber asphalt, impregnated fabrics and other substances, including antimildew polish and irritating footpowders may be at fault Shoes may be tight ill-shaped or impervious to sweat and so cause skin disorders on the feet. Not all rashes on feet are due to fungi. Rubber is the usual irritant the antioxidant the likely irritating ingredient thereof in thermoplastic box toe shoes (Shatin and Reisch ADS 69 631 1954)

See Niles (J 110 343, 1938) Burgess (CanadMAJ 47 27, 1942) Schwartz (PHRpts 51 423, 1936) wrist watch strap Pirila (abs BJD 60 147 1948 hatband thioprene in artificial leather

COSMETIC DERMATITIS.—Cosmetics including perfumes, hair dyes scalp cleansers, and tonics, depilatories, deodorants, face powders, creams bleaches, lotions, rouge, lipstick and nail preparations may contain many potentially provocative chemical constituents (Tulipan ADS 38 906 1938)

Compositions and hazards of numerous cosmetics were briefly elucidated by Wolcott (ADS 41 64, 1940)

See Chilson (Modern Cosmetics, Drug and Cosmetic Industry N Y., 1934) Harry (Modern Cosmeticology Hill London, 1948) Lynch (MinnM 20 519 1937) main features of cosmetic dermatitis Downing (ADS 64 561 1951) dangers of dyes, cosmetics and permanent wave chemicals on scalp and hair Behrman et al (J 140 1208 1949) cold wave process generally safe Schwartz (I ternat Congr Allergy 1951 p 715) skin testing and prophetic patch testing of each kind of cosmetics.

A typical dermatitis paralleling the blepharal margins is produced by the antioxidant of the rubber of eye lash curlers (Curtis ADS 52 262, 1945) Lipstick dye may cause systemic allergic phenomena as well as cheilitis (Hecht J 113: 2410 1939; Zakon et al.: ADS 56 499 1947) Dentifrices provoke cheilitis and dermatitis of the cheeks and chin, and even dermatitis of the hands at times (Belshauser ADS 41 693, 1940) The yellow dye of a leg make-up was the faulty ingredient identified by Ellis (ADS 49 197 1944) Hair lacquer caused much trouble at one time the irritant being synthetic resins (Schwartz: PHRpts 58: 1623, 1943) and the mother's hair lacquer irritated her infant in 2 cases recorded by Plotz (AmJDisChild 68: 409 1944) Hair dye poisoning, even a fatality was discussed in an interesting editorial (BMJ 2: 490, 1943)

In nail lacquer a formaldehyde-sulfonamide resin caused cases of Simon (SouthMJ 31: 157 1943) while nitrocellulose and solvents, as well a synthetic resins were noxious in cases of Dobes and Nippert (ADS 49: 152, 1944; see also Madden: ib 49: 19, 1944; Osborne et al. ib. 44: 604 1941 Silver a l Chicago JID 9: 361 1929) Nail lacquer dermatitis rarely affects the hands but provokes circumscribed lesions readily confused with parasitic rather than chemical dermatitis of the areas to which fingers go such as eyelids, ears trunk, and vulva. A pruritic patient with any dermatosis such as scabies, is well advised to omit nail lacquer until her skin is clear for where she itches she will scratch, and she may develop nail lacquer dermatitis as a complication. Nail lacquer dermatitis was the subject of interesting studies by Keil and VanDyke (ADS 50 20 1944) in whose patients the chief irritating ingredient of the lacquer was a toluene formaldehyde-sulfonamide resin. Group sensitization to related chemicals was frequent including sulfonamides and formaldehyde





Fig. 105 —Dermatitis venenata caused by leather hatband. (Dr F Ronchese)
Fig 106 —Dermatitis venenata of face caused by hair dye. (Dr Howard Fox)



Fig. 107 —Personal contact dermatitis such as might be caused by lipstick, dentifrice, chewing gum medication. It was caused by nail lacquer (Dr Wm. L Dobes)

Hair lacquer for upsweep coiffures may cause dermatitis of ears, neck and eyelids (Howell J 123 408, 1943; Epstein: ib., p. 409 Halley SouthMJ 37: 37 1944; Schwartz AnnAllergy 1 16. 1943) Lacquer pads are often at fault, likewise spray net, etc. Ink eradicator may contain sensitizing lacquer (Dowling ADS 44 465 1941)

Base coat for fingernails, composed of phenol formaldehyde resins and synthetic rubber in methyl ethyl ketone often caused in 1948 and 1949 hypertrophy of the nail bed and onycholysis, usually painless and without indications of inflammation These changes disappeared from clinical view when the cosmetics were removed from the market. Patch test results were various, and allergy seemed not to be the explanation. See Onycholysis also Winston and Sutton (JKansMS 49 3 1948); Layman and Rusten (MinnM 31 L.15, 1948), Sulzberger et al. (JID 11 67 1949) Sullivan (BullJHHosp 84 11 1949) Hein and Rogl (ADS 61: 971, 1950) Framess et al. (J 149 828 195.)

Jewelry dermatitis is likely to be due to nickel, chromium lacquer or the accumulation of irritant chemicals underneath, such as soap under rings (QMN J 144: 725, 1950)

Hair dyeing with synthetic organic dyes of the paraphenylenediamine group was discovered about 1890, according to Thomas (Pract 165: 171, 1950) This group of chemicals contains potent sensitizers. Sensitization is slow to develop and patch tests should be performed prior to each application, even in persons who have not previously reacted (Lawrence: JID 8: 177 1947) Hair dyes have produced much less dermatitis since 1937 than before that time because of improvements in their manufacture the prophetic patch test, and instructions on the package requesting predyeing open patch testing regulated by law the modern paraphenylenediamine dyes are not unduly hazardous (Schwartz and Barban: ADS 66: 233, 195_) Reiches (ADS 63: 619 195_) reported 3 cases, however

Permanent waving requires softening the hair with an alkaline sulfide followed by heat setting and then rinsing, or a cold process with thioglycolate followed by an oxidizer (Goldman et al.: J 137: 354, 1948) Cold wave chemicals are usually innocuous the beauty operator standing greater hazard than her client. The possibility of allergic response to wetting agent and perfume ingredients always exists as well as to the essential waving chemicals (Lehman: J 141: 84_, 1949) Ammonium thioglycolate in the concentration advised for home waving is seldom harmful if used according to directions (Brunner: ADS 65: 316 195_) If the softening solution is applied too long or too concentrated, the hair may break off, producing temporary baldness without dermatitis followed by normal regrowth (Reiches and Lane J 144: 303 1950) Permanent wave solution once ran into an ear canal and perforated the drum reported Sataloff and Wilson (J 14 : 1183 1951)

Hair straightener is powerfully alkaline and burns from it may produce depigmentation (Lewis: J 11 : 86 1939)

Miscellaneous cosmetic irritants include the following methyl heptine carbonate, perfume at one time popular in lipstick (Baer ADS 32 726, 1935); Lash Lure (Bureau of Investigation J 101 1916, 1933); triethanolamine a wetting agent which is seldom injurious (Curtis and Netherton ADS 41 729 1940) rubber sponges used for applying cosmetics (Furman et al. JID 15 223, 1950); blue toilet tissue (Brattman: ADS 65 737 1952) monoglycerol para-aminobenzoate the sun screen ingredient of T rtan, occasionally a violent irritant, requiring in my experience no 7-day incubation period to blister the patient (Fatelsky ADS 62: 711 1950); Teel, a liquid dentifrice, producing maculation on fingers (Hix ADS 43: 847 1941); liquid lip rouge (Schomberg ADS 45 18_ 1942); citronella oil (Keil JID 8: 327 1947) aminoazotoluine, a yellow, fat-soluble dye used in shoe polish and semisolid inks for ball-point pens (Mears and Mortis-Scott: BMJ 1 1143, 1953)

Industrial and Occupational Dermatitis.—Since dermatitis venenata is of vast significance in industrial medicine its control assumes important proportions; and its recognition, prevention and treatment have been the subject of intensive study (Schwartz et al Occupational Diseases of the Skin, Lea & Febiger 1947) The principles of interpretation are those of contact dermatitis. The principles of treatment are in general, the prevention of contact by avoidance use of suitable protection such as gloves, chemical detoxification of harmful substances before they have produced damage identification of noxae as well as susceptible employees by means of patch tests and similar testing of materials before they have been admitted to public use

Recognition of occupational dermatitis, the definition of primary irritants, the identification of sensitization thresholds and the prevention of dermatitis were elucidated by the report of the A.M.A. Committee on Occupational Dermatoses (J 122 370 1943) Instructive papers on working out specific problems were presented by Schwartz (SGO 68 58 1939) Stigmas of occupation, such as scars and calluses, were interestingly collated by Ronchese (J 128 925 1945)

See Downing (NEngJM 237 788, 1947) and Schwartz (JMo MA 42 771, 1945), Lane et al. (J 118: 613, 1942) Birmingham and Campbell (Occupational and Related Dermatoses, Public Health Publication #364 Govt. Print. Off 1954) abstracts literature 1943 1953

The difference between poisonous (or toxic) and allergic reactions is essentially a difference in degree of toxicity Toxic and allergic reactions cannot be distinguished except by differences in quantity of noxa argued Anderson (IndustM 12 584 1943) While desensitization cannot be achieved, yet there are chemical antidotes for some kinds of poisoning Spontaneous desensitization does occur however (Koch abs J 121 87 1943) see Hardening

Pre-employment examinations are helpful in screening out persons with dermatoses liable to aggravation by contact with the substances to which the proposed occupation will subject them. A clean shop with good ventilation and neat housekeeping shielded and modern machinery, tidy showers, cleansing facilities and locker room—all contribute to health of the workers and prevention of dermatitis. See Edit. (BMJ 1 277 1949)

INDUSTRIAL DERMATITIS, DIAGNOSIS.—As part of a symposium concerned with the problems of industrial dermatology Sulzberger and Finnerud (J 111 1028 1938) contributed this clarifying tabulation:

CRITERIA OF THE FIRST ORDER FOR PROOF OF INDUSTRIAL NATURE OF DERMATOSIS

Inception.—The dermatiti appears at any time during a period of *industrial ex*posure or even after a lapse of a reasonable incubation period following the cessation of the industrial exposure (usually a maximum of from to 3 weeks)

Amelioration.—The dermatitis regularly disappears or i repeatedly impro ed within a reasonable period of days, weeks or even months aft r cessation of the causal industrial exposure While this is usually the case retention of causal agents, complication or ensuing polyvalent sen itization may prolong the course even for several years after the last industrial exposure

Recurrences and Exacerbations.—The dermatitis shows a tendency to recur or to become exacerbated when the worker returns to the identical industrial exposure afte a period of absence provided there ha been no change in wo king conditions, in the pa tient s manner of working or in his susceptibility

CRITERIA OF THE SECOND ORDER: ADJUVANT CRITERIA

*The dermatitis appears first in the areas of maximum exposure and is usually con*fined to them. In a small percentage of cases it spreads to appare tly unexposed areas or may begin there o m y even become generalized.

The character and localization of the dermatitis correspond to the character and localization of dermatiti known i oth r cases to have been caused by exposure to the same or similar industrial hazards. While many different substances and procedures can produce similar or identical eruption there are certain classes of subst nces and of procedures which regularly produce fairly characteristic lesions.

The application of the presumptive *causal age ts to an u affected site close to the* site of the dermatitis produces a reaction, provided this application is made either during the active phase or after the proper interval following the cessatio of th dermatitis.

The cuta eous tests produce reactions of the same fundamental nature a the derma tosis under i vestigation.

Othe workers similarly occupied are or have been imila ly affected.

The dermatitis appears soon (days or weeks) after the patient begins work involving ew potential hazards.

The dermatitis i proved to be of possible occupational ature; that is, it is shown to be of the type which may result from the industrial exposure sustained. I this con nection it must be determined that the dermatiti der consideratio is not a no industrial dermatosis, such as seborrheic dermatitis, psoriasis (including pustular psorias) para psoriasis, lichen planus dermatitis herpet formis, m ltiform erythema certain types of nonindustrial fu gous and other infectious processes, nonindustrial impet go and other pyoderma acrodermatitis continua, nonoccupational drug eruptio s, herpetic eruptions, nevoid anomalies or malformations of the skin, nonindustrial dermatitis exfoliativa, cir cumscribed ne rodermatitis, atopic dermatitis and, particularly noni dustrial co tact dermatitis. It must be borne in mi d that the prese ce of nonindustrial dermatosis by no means excludes coexistence of ind strial dermatitis. The existe ce of nonin l strial derma tosi may pred pose to industrial dermatitis and, on the othe hand, industrial exposures may elicit attacks of such noni dustrial dermatoses or prolong their courses or prod ce exacerbations of them.

THE DERMATITIS IS ERRONEOUSLY CONSIDERED TO BE NONINDUSTRIAL BECAUSE

It is accompan ed by the fi ding of fungi or other microorganisms in the lesions or a a distant focus. Fungi, pathogenic and nonpathogenic, and certain other microo gan sms, e.g staphylococci streptococci, yeasts and molds, re almost u i ersally found on the ki of ad lts in the United States. Their demon tration does not constitute proof that a dermatos s of onoccupational nature.

It i accompanied by a c taneous reaction to test with extracts of fungi or of ce tain other microorganisms. Such reactions are too common to be of weight in ruling out the ind strial nat re in a given case they merely show that the patient has previousl had se sitizing exposure to the same microorganism or to one immunologically related to it they are comparable to react ons to tuberculin in the general population.

The reactions to patch tests with the substances f the ind strial exposure are nega tive. Such egat ve results of patch tests cannot be consid red conclusive. They may be due t (a) local diff re ces in sensitivity The areas tested may not be hypersens t ve while othe areas, part cularly the areas involved, may be hypersensitive. (b) Chronologic differences n sensit vity A person s skin, sensitive at the time of i dustri l conta t may be no sensit e to th a tual causal subst ces t the tim of test g c) The fact that the ctual causal substance r substances, o the ca sal combi tion, o causal inter mediates may not have bee ppl ed. (d) The fact that the concentration employed may have bee too weak, that th test application may hav been otherw se inadequat or that the vehicle employed may have been i correct o ma have preve ted penetrat on r e erted some *protective o neutralizing effect;* e.g water instead of sweat, fat or oil i stead of aa queous vehi le or vice versa acid instead f alkali or vice versa. (e) The fact that the test neve accurately reproduces th actual conditions of ind trial exposure.

Repeated contact friction maceration heat cold, sweat or other industrial agents or processes may be necessary additional factors enabling the substance, giving negative results in the test to cause dermatitis under the conditions of industrial exposure.

THE DERMATITIS IS ERRONEOUSLY CONSIDERED TO BE INDUSTRIAL DISEASE:

It is a dermatitis affecting a worker in an industry notorious for the occurrence of that type of dermatitis. For example dermatitis venenata may be due in the specific case to nonindustrial exposures home exposures to dyes, cosmetics toilet articles, insecticides, clothing paint varnishes or plants, or exposures to substances encountered in avocations such as photography painting or sports.

It is accompanied by a reaction to a patch test with a substance or substances encountered in the industry. Such a reaction to a patch test cannot be considered conclusive (a) it may be due to the application of a primary irritant or of a primarily irritating concentration; and (b) since the test never accurately reproduces the conditions of actual industrial exposure a reaction may mean simply sensitivity of the skin to a certain substance when applied in a certain concentration and manner at a certain time to a certain site while the same substance may be incapable of causing dermatitis under the actual conditions of industrial exposure and (c) see Latent allergy

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INDUSTRIES COMMONLY AFFECTED.—Workers in certain trades are prone to skin eruptions, and many cases are seen in connection with the Workmen Compensation Act. Analyzing more than 500 occupational cases Klauder (ADS 48 570 1943) found the causes fell in the category of trauma in one-fourth, primary irritant in one-fourth cleansing agent in one-sixth sensitizers in one-eighth, and petroleum products and water maceration in about one-tenth each. Specific causes found in more than 3,700 cases were reported by Klauder and Gross (ADS 63: 1 1951) Wet work and the methods of cleaning the hands were especially important factors. Exposure of the hands to alkali diminished the normal acid mantle for almost 4 hours. Over 3,000 cases were surveyed by James and Bleiberg (JIMSocNJ 46 445 1931) Etiologically their cases were classed among those due to primary irritants, sensitizers trauma wet work maceration cleansers, petroleum products, infection and miscellany

CEMENT WORKERS are likely to be harmed by alkali. Lime is slaked in perspiration on the skin which becomes dry hard, thick and liable to painful fissuring Ulcers of the nasal mucosa as well as of the skin, may result. Secondary infection with mycotic or coccic organisms is likely Prevention lies in control of dust and cleanliness of the workers. Goggles protect the eyes, talcum helps keep the skin dry (Lether BMJ 2 702, 1937) and boric ointment protects the nostrils (Meherin and Schomaker J 112 1322 1939) Chromates in cement may account for some cases of cement allergy and a patch test with chromium should be made (Spier and Natzel AfDuS 193 537 1952) Chromium was found but not in great quantity in two-thirds of the various German cements tested.

FOOD HANDLERS.—Cleansers and detergents take their toll among these people Chrome ware and polishes are handled by restaurant employees, who also may wash dishes and come in contact with the sometimes irritating sterilizing chemicals that city health departments require such as Microlene (Sterling J 127 219 1945) Waitresses have the same kinds of dermatitis of the hands that affect other women, with their creams, lotions and nail lacquer Cooks are subject to irritation by flour and flavorings as well as burns which would be trivial if not mistreated. Baker s eczema has often been caused by ammonium persulfate a flour improver (Prakken and Postma NederlTijdschr 1938 p 367 Zündel and Jentsch abs YBD 1939 p 100 Jentsch abs YBD 1941 p 65) Sensitivity to this is sometimes lost when the chemical is avoided for a year or two Flour may act as an inhalant sensitizer giving rise to positive skin tests to wheat oats or rye (VanDishoeck and Roux abs YBD 1940 pp 113 114) and urticarial lesions, different from what ammonium persulfate causes (Id JAllergy 12 481 1941) Vanilla was reported to be an allergen to which some workers became hardened by Gougerot and Basset (ReocfrancD 46 1329 1939) Cinnamon is a common irritant (Epstein Ohio MJ 46 659 1950) it may reach the skin of the hands by way of a tooth paste (Leifer ADS 64 52, 1951)

See Contact Photosensitization, Plant Dermatitis; ... Frank (ADS 33 ... 1936) beef ... Newton (ADS 34 ... 1936) chicken blood, OMN (J 132, 894, 1946) chicken pickers and fowl mites Hopkins (MarylMJ 1 ... 1952 ADS 67 ... 1953) mushrooms ... et al (AnnAllergy 4 ... 1946) mango Burks (AnnAllergy 12 ... 1954) onion and garlic dermatitis in housewives Morris (IndustMed 23 ... 1954) trauma, over treatment, soaps, detergents and tinea causing dermatitis in food handlers.

Glass Wool, Fiberglas and Similar Spicular Irritants.—While the mechanical irritation of spicules is a major element in causing dermatitis, the alkaline content of rock wool made by *blowing air and steam through molten* blast furnace slag or silliceous rock, is also of consequence (J 113 1756 1939)

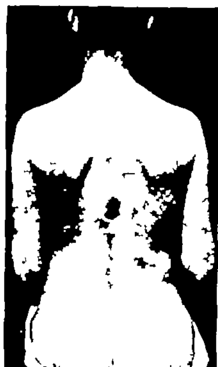




Fig 108 —Cement dermatitis (Dr Howard Fox)
Fig. 109 —Chrysarobin dermatitis (Dr D B H. Cleveland)







Fig. 110 — Asbestos corn (*Alden and Howell ADS 49 312, 1944*)
Fig 111 —Fibers of amosit asbestos (Alden and Howell)
Fig 112 —Foreign body reaction to asbestos fibers (Alden and Howell)

These substances are used for insulation, packing cushions, and the manufacture of textiles for garments and seat covers. They may be treated with synthetic resin fillers, which may sensitize (Schwartz ADS 55 258 1947)

Fiberglas may incite dermatitis of consequential severity traumatic and usually occupational affecting especially xerotic blond persons. The forearms legs, flexures and groins become red and itchy following exposure, but

not vesicular as in allergic contact dermatitis. The rash is transitory and dry. Washing with water immediately after exposure reduces irritation, but some persons cannot work with the material. Contaminated clothing may incite dermatitis in other persons, and spicules on the worker's skin may be transferred to members of his family by way of the bed linen (Pellerat abs YBD 1947 p 581). No sensitization was proved by Sulzberger et al. (IndustM 11 482, 1942).

Protective clothing and greases are not effective in controlling this microtraumatization, but changes of garments, good ventilation, loose work clothes and the free use of showers without soap immediately after exposure will succeed. See Hein (J 124 187 1944).

Pyrotenex, an electric conductor consisting of copper tubing packed with glass fiber produces similar trouble. Ward (BMJ 1: 905 1952) observed glass spicules protruding from the skin in his patients. Tight sleeves, a barrier cream and rinsing the forearms with running water prior to washing with soap are measures helpful in control (Cameron BMJ 1 1240 1952).

Miscellaneous Industries, Irritants and References

See Schwartz, Tulipan and Peck (Occupational Diseases of the Skin Lea & Febiger 1947)

Agriculturists	poison ivy, ragweed, other plants; ticks chiggers; *fertilizers*, sprays, insecticides, fungicides, milk can cleansers, irritant soaps, chlorine in privies; sunlight, causing cancer
Aircraft manufacture	zinc chromate primer resins, glues oil acid fumes (Hall: J 125: 179 1944)
Automobile workers	cutting oils, solvents, brake fluid, paint lacquer
Bakers	flour or sugar; cottonseed oil and potash, the former being used in bread, the latter in pretzels whitening agents; essential oils of flavoring
Barbers, Hairdressers	quinine mercury capsicum arsenic, sulfur Cantharides, various dyes and cosmetic substances
Briquette makers	coal tar pitch, causing photosensitivity melanosis, tar acne keratoses, epitheliomas
Butchering	anthrax, foot and mouth disease, erysipeloid, hog itch, acute pemphigus, onycholysis from pancreatic juice verruca necrogenica
Candymakers	sugar chocolate cinnamon, oil of cassia, citrous oils, vanilla, other flavoring agents
Canning	fruits, vegetables, citrous oils, peach juice and fuzz, pineapple juice, figs, tomatoes, potatoes, carrots and lettuce
Carpenters	various woods, sawdust, plywood adhesives
Chemists	many irritants handled by them
Cigarette paper	dermatitis of fingers (Tye JID 14: 77 1950)
Citrous fruit industry	trauma, maceration, paronychia, monilial interdigital dermatitis, lemon oil irritation, dye hazards (Beerman et al. ADS 38: 225, 1938 Birmingham et al.: AIndustHyg 8: 57 1951)
Coal miners	no particular specific occupational dermatitis. Feet should be kept dry. Good ventilation, efforts to reduce dust, and early reporting of the presence of disease advised (Knowles BMJ 2: 430 1944)
Compositors	benzine, bichromate
Cooks	cleansers, soaps, insecticides, flour bleach (benzoyl peroxide)
Cosmeticians	cold wave thioglycolates, hair dye (paraphenylenediamine) cuticle softeners, nail lacquers, hair bleaches and shampoos
Dentists	local anesthetic chemicals, soap, prosthetic plastics, metals
Dermatophytosis in industry	see Downing (J 125: 196, 1944)
Diesel engine workers	rust inhibiting bromate dermatitis, treatment with 3% BAL in zinc ointment (Cole J 140 718, 193_) hydrocarbon solvents and chrome are major problems (Guy ADS 70 239 1954); see Plunkett (Min M 37 330 1954)
Electricians	chlorinated hydrocarbon dielectrics
Electroplaters	cyanide various acids, chromates
Electrotypers	copper sulfate hydrochloric acid
Explosives manufacturers	T.N.T. tetryl, picric acid and picrates, mercury fulminate, ammonium nitrate (Schwartz J 1_5: 186 1944); see War Material (p. 150)

Exterminators	arsenic formaldehyde fluoride lead, Pyrethrum, DDT
Finger paint	see Tobias (J 13 : 533, 1949)
Fish i dustry	trauma and infection, bites redfeed dermatitis (Schwartz and Tabershaw: JIndustHyg 27: 273 1945)
Fi bermen	bites, abra ions, stings infections
Foresters	poisonous shrubs sprays, repellent
Furriers	arse ic d estuffs, i secticides
Gasoline	toxicology see Maeble (J 11 : 1963 1941); Biederman (J 106: 2236, 1936)
Glue	resin glues in wood man facture: protei glues, natural resin glues synthetic resin gl es, combination ; urea an l phenol formaldehyde resin dhesives cause most of the troubl in maki g plywood. Control measures protective cloth ing cl an ing facilities, hardening Alkaline gelatin; phenol formaldehyde urea formaldehyde styrene alkyd allyl resin (Schwart et al.: PHRpts 58: 899 1943)
Grocers	sugar a d flour cleansers roach powder
Ink, fl escent i vi ible	see Bloom and Weiner (JID 11: 197 1948)
I terior decorators	dyes a d fabric fini hes
Laboratory workers	infecti ns acquired in laboratories; re safety measures, see Sulki and Pike (J 147: 1740 1951)
Laundry work rs	alkaline soaps, sy thetic det rgents, antiseptic after rinses (phenyl mercuric compound) bleaches
Machine tool operators	cutting il cleansers, antiseptics i oils
Milliners	dyes, arsenic
Nurses	mercury formaldehyde medicated alcohol, l resol other antiseptics morphi penicillin, streptomyci soap cosmetics
Painters	turpentine solvents, arsenic linseed oil dyes, alkali pai t removers
Petroleum workers	oil, gasoli e clea sers
Pharmaceutical wo k rs	see Dalton a d Pi rce (ADS 63: 60 , 1951)
Photoengraving	ld aniline brom um alkali formaldehyde glue
Photographers	pyrogallol M tol c stic soda chromates dyes, lacquers, colo process chemical d sensitizers (Wei sberger: Sci 110: 438 1949)
Ph icians and surgeons	contactants, infections radiation i jury (Epstein J 147: 1751 1951); antiseptics, local anesthetics rubber gloves trauma from scrubbing
P neapple d stry	proteol tic enzyme, brom li removes epidermis of finger tips, calci m oxalat needles cause mechanical damage and itching (Polo i : BJD 63 441 1951)
Plate print rs	inks solvents d es, cleansers (Neal a d Emmons: PHRpts 54: 89_, 1939)
Polishers f m tal	oxalic cid, turpe tine bichromate
Pott ry wo kers	cobalt put into wet clay to ne tralize color of yellow iron oxide impurity (Pirilä ActaD-V 33 193, 1953)
P t rs	arsenic artificial coloring hydrocarbon i i k chromate in photostats, cleansers
Railroad h ps	petroleum chlorinated hydroca bon solv ts, chromates in f el oil cra kcase oil a d coola ts. Control by suitable cleansi g protecti clothi g protective cream, educa tion of wo kers (Schwartz JIndustM 1: 10 492 195_) See Diesel engine workers.
Seamstresses	t xtile finishes, d es, wool, thread, yarn
Shoemakers	chrome-tanned leather dyes, cements, polishes solvents, rubber See Clothing shoes nd leath goods.
S lk ha dl rs	antimildew m y irrit t (Goodman Diseases of Tradesmen, by Ramazzi i, Medical Lay Press, 1933)
Stenographers	cleansers cosmetics (rarely carbon pape)
Tanners	b chromat hydrochloric acid
Toilet seat	from pa nt antisept cs, detergents varnishes (Tulipan In du tM 9 303, 1940)
T rpentine	terpene derivat ves, pinen, camphor menthol, eucalyptol; oxidat on of stored turpent ne makes t more irritati g than the fresh substance (McCord J 86 1979 1976 Riedel KB Wchn 19 1034 1940; R kst d BJD 59 115 194 ; Hellerstrom and Lunden abs YBD 1951, p 145; Hellerstrom a d Thyresso ActaD-V 23 51 195_)
Weld rs	actinic burns, hromium fumes, zi c hloride ammonium chloride, fluoride fluxes
Wood preservatives	phenyldichlorarsine; thyl mercuric phosphat etc. (Sayers and Dudley: PHRpts 53 1209 1938; Vintinner: JIndust Hyg 22 297 1940)

INDUSTRIAL DERMATITIS.—MEDICOLEGAL ASPECTS OF OCCUPATIONAL DERMATOSES constitute a specialty within themselves. The physician, being an expert witness and not a lawyer, is called upon to give his views as clearly and accurately as he is able, and to play no favorites.

An attorney in selecting a physician to serve as an expert witness will appraise his competency integrity experience and ability to articulate (Enggas, pers. comm., 1953) Strict neutrality is a difficult but advantageous position to maintain, for the cross examiner can use bias in the expert effectively to discredit him. Decisions regarding what is occupational dermatitis and what is not, and how much disability has been caused and what compensation is just are the prerogative of the commissioner or the jury The physician possessed of special medical knowledge and good case records will influence the judgments rendered but has no further responsibility for them His opinions will carry weight proportionate to the clarity of his thinking his investigation of the case and his presentation of the facts, but he owes nothing more than the whole truth as he sees it

The physician called to the witness stand is well advised to be humble, careful and deliberate He may ask for restatements of complicated questions. He should give his attorney time to rescue him by objections when interrogation becomes too tense He cannot argue successfully with those who argue professionally He will find his cross examiners remarkably well informed, well prepared and able at their work opponents not to be underestimated capable of confusing and distorting what he says, best countered by courtesy an even temper careful patience and adherence to facts.

One may rightly assume that in a courtroom a good attorney can make a dupe of a good doctor One may remind a doctor that he has the right to decline or accept a case but that once he has accepted he is in it all the way

I formatiy articles on medicolegal aspects f occupational dermatoses re those by Downing (J 111 1518, 1938 ADS 39 12, 1939) Foerst (J 111 1842, 1938) Sulzberger (BullNYAcadM 18 665 1942), the M. D. and ross examination QMN (J 151 1052, 1952) answers on "spreading of llergic base, regard as whether occupational disease results in llergy to other substances Viscount Simon (BMJ 2 1 1953) the loctor on the witness stand Curphy (J 154 457 1954) preparation of medicolegal case Souder (Sci 119 819 1954) effectiv expert testimony techniq; Gilbert (J 156 1311 1954) courtroom comportment

INSECTICIDES AND REPELLENTS—*Pyrethrum and rotenone (from derris)* are substances valuable in insect control but they are sensitizers (Martin and Hester BJD 53 127 1941 Dorne and Friedman J 115 1268 1940) Sta Way caused not only a general rash but also nephrosis and edema in a case of Hoehn (J 128 513 1945) and Flit was the irritant containing oil of lemon, turpentine and pyrethrum in a report by Simons (abs J 114 95 1940) DDT with its valuable power of remaining insecticidal for a long time can continue for an equally long time to induce allergic dermatitis, as in a widespread case of eczema which lasted nine months after spraying (Leider JID 8 125 1947) and in one of exfoliative dermatitis (Higgins and Kindel JID 12 207 1949) The patient of Hollander (ADS 62 66 1950) allergic to DDT had not only an extensive severe rash but also areas of actual necrosis.

See Schwartz nd Warren (PHRpts 54 1426, 1939) on naphthyl isothiocyanate Simons (ActaD-V 28 601, 1948) on dermatitis, mucosal irritation, umbness, vomiting, even deaths among workers in derris mills Goldman (ADS 62 246, 1950) reviewing chemistry and dermatologic aspects of repellents Campbell (BMJ 2 415, 1952) neurologic langers of DDT See also Scabies and Pediculosis

MATCHBOX DERMATITIS.—Intolerance of the phosphorus compound on the striking surface of matchboxes is by no means rare. The lesions it produces are typically dry reddish scaly itchy ones, likely to be located underneath the pocket where matches are carried Conveyed by fingers, which are heavily contaminated in pipe smokers particularly it may cause dermatitis of the face, neck and hands sometimes, though the chest or the thighs and scrotum are the usual sites. Klaber (BJD 50 451 1938) reporting a case reviewed the literature and stated that P S is the active agent. He noted the abetting influence of moisture and warmth as well as allergy A patient of Wilson (NebrSMJ 18 183, 1933) acquired allergy to matches only after the head of a match burned

the finger tip beneath the nail The ears were principally affected in the patient of Templeton (ADS 44: 676 1941) the face in cases of Burgess (CanadMAJ 65 567 1951) Martin (abs BJD 63 39 1951) saw many instances in a matchbox factory While only dermatitis disturbed two patients, one had systemic poisoning of consequence as reported by Burgess (Canad MAJ 65 567 1951) When a lighter is substituted for matches one must think of the possibility of allergic response to lighter fluid.

Medicines are common causes of contact dermatitis. They include both primary irritants and sensitizers. A dermatologist must remain keenly alert to the possible ill effects of medication applied to skin or mucous membranes, for he sees daily in his patients the damage done by substances applied by the patient by other physicians, and even by himself.



Fig 113.—Dermatitis of eyelids from matches. (Dr D. E. H. Cleveland.)





Fig 114—Matchbox dermatitis. (Dr D E H Cleveland.)
Fig 115—Matchbox dermatitis. Close-up of Fig. 114

See medicinal irritation, the chapter on Treatment, also Prystowsky (SouthMJ 45 960 1952) Sulzberger and Wise (ADS 28 462, 1933), Gaul (J 127 430 1945); Underwood et al (J 130 249, 1946) Underwood and Gaul (J 138, 570 1948) overtreatment Bae et al (AD 71 19 1955) sensitivity index of various topical therapeutic agents Gaul (J 157 720, 1955) overtreatment, especially of contact dermatitis, worst offenders among medicines re mercurials, sulfonamides, local anesthetics, antihistamines

Adhesive Plaster.—At one time containing orris root a common sensitizer adhesive tape has been greatly improved. The mechanical effects should not be overlooked (Pinkus: JID 16: 383 1951) nor the possibility of confining pathogenic bacteria or molds and sweat under tape (Humphries JID 9 219 1947 Gaul and Underwood: JID 12: 173, 1949; Peck et al. ADS 63 280 1951) Composition of adhesive plaster and reactions thereto were reported on by Schwartz and Peck (PHRpts 50: 24, 851, 1935) See also Sheldon et al. (JID 4 295 1941); Franks (JAllergy 17 112, 1946); Kell and Bereston (ADS 45: 105, 1942) The irritating rosin often has come from abietic acid a turpentine derivative.

ANESTHETICS, TOPICAL.—Orthoform put into a tooth socket caused a generalized vesicular and urticarial rash (Hein and Feldman: UCutRev 38: 871 1934). Saline in leaking from gluteal m scle to skin of a patient given bismuth injections for syphilis produced contact dermatiti (Brunsting and Brs ting ADS 36: 118^ 1937 Nupercaine i a frequent ca se f dermatitis (Pantus: J 101: 30 1933) and few dermatologists prescribe it. Halley a d Halley (ADS 36: 1084 1937) were among the first to condemn it. Interesting studies of sensitization to the procaine group have been given by Goodman (JID



Fig. 116.—Cement dermatitis. (Dr Sam E. Sweitzer)

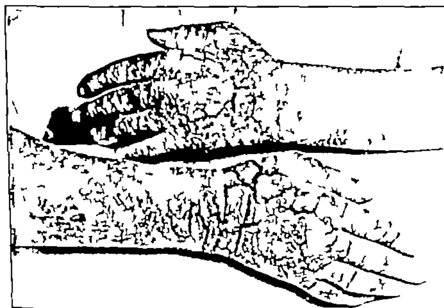


Fig. 117.—Severe dermatitis of the hands and forearms in grocer

53, 1939) Rein and Kanof (JID 11 311 1948) and Lane and Luikart (J 146: 717 1951.) Procaine Orthof rm, llutes Pi rat tetraca (Pontocai e) dibucaine (N per cai e) ethyl aminobenzoat (Benzocain) X lcain Apothesine Larocaine, nd Metcaine are members of the group. They are occupat o lly hazardou to dentist especially (Laden a d Wallace: JID 12 299 1949) although I see more dermatitis of th ha ds in denti ts caused by soap tha h llergy The eyel ds of patients nd fingers of ophthalmologists suffered Pontocaine dermat tis reported McAlpine and Berens (AmJOphth

25: 706, 194) and the use of local anesthetic substances in eye disease is being criticized nowadays. *Procaine accounts for some cases of seeming intolerance of penicillin* (Hitschmann et al.: JID 15 105 1950)

The antihistamine ointments are local anesthetics but generally do considerably more harm than good. See Treatment antihistamines. Sidi et al. (ActaAllerg 5: 292, 1953); Nomland (JIowaSMS Apr 1953)

ANTIBIOTICS.—Contact dermatitis evidently primary irritation was reported from bacitracin (Reisbea ADS 63 304, 1951) and from Chloromycetin (Robinson et al. JID 1 ?03 1951). Tyrothricin and other antibiotics irritated a patient of Goldman et al. (JID 11: 43 1949)

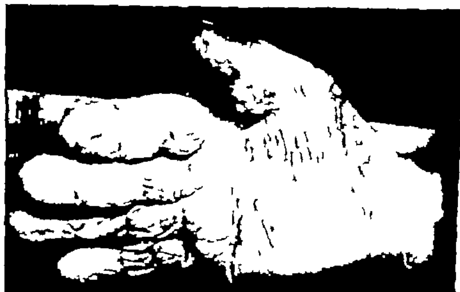


Fig 118.—Iodoform dermatitis



Fig 119.—Vesicular dermatitis caused by a fungicide

Penicillin ointment has been abandoned for it is often a primary irritant as well as a sensitizer and is especially likely to rouse intolerance if put on the skin and given parenterally at the same time. The dust on the hands of a man who dispensed penicillin caused facial and genital dermatitis, reported Pyle and Rattner (J 125: 903, 1944). Penicillin eye drops blistered the eyelids in Bedford's case (BMJ 1: 51, 1946). Epidermal sensitization appeared in 9 of 200 patients tested by Gottschalk and Weiss (ADS 53 863, 1946). Dermatitis among workers engaged in producing penicillin was reported on by Friedlaender et al (ADS 54 517 1946)

Streptomycin is an epidermal sensitizer affecting especially the nurses who handle the drug (Strauss and Warring JID 9 3, 90 1947; Berke and Obermayer: JID 11 253, 1949; Crofton and Foreman BMJ 71 1949; Touraine and Pichon PresseM 56 ?63 1949). About half the personnel frequently exposed to it develop contactant allergy. The eyelids and uncovered skin are principally affected.





Fig. 120.—Dermatitis venenata following application of belladonna plaster (Drs. John A. Fordyce and George M. MacKee.)

Fig. 121.—Medicinal contact dermatitis, from iodine. (Dr Howard Fox.)



Fig. 122.—Blistering from tincture of iodine applied as home remedy for "rheumatism." (Dr D. D. H. Cleveland.)

BUTESIN PICRATE is a notorious offender first reported as causing acute vesiculobullous dermatitis with erythema by Pusey and Rattner (ADS 10 917 1929); see Edit. (J 109: 902, 1937) for many cases with bibliography. The hypersensitivity is quite specific, being limited in the case of Laden and Rubin (JID 11 119 1949) to the alkyl esters of para aminobenzoic acid.

IODINE occasionally is intolerable, causing an acute violent, vesicular dermatitis. Its percutaneous absorption is rapid and topical application may be followed by the same rashes as follow sometimes its internal administration (Clifford BostonMSJ 193: 931 1920). Death ensuing from the application of iodine to the skin was reported by Alexander (BMJ : 100 1930). To remove iodine from the skin (or clothing) use a 1% aqueous solution of sodium thiosulfate the specific treatment for iodine burns (Sutton ADS 33: 100–, 1936). Patch tests on 5 persons sensitive to iodine evoked general reactions in 3 of them (Lelner: JLabClinM 7: 1151 194).

MERCURY.—Intolerance is common. Clinical experience suggests that about 1% of dermatologic patients cannot use it. Percutaneous absorption is a hazard: yellow oxide killed a psoriatic patient of Greuer (DWchr 111: 939 1940). Severe reactions in children concerned Gibel and Kramer (AmJDisChild 60 153 1943) for not only dermatitis but also fever albuminuria and lymphadenopathy may be produced (Samitz ADS 50 10 1944). See The Pink Disease. A severe case of intolerance of ammoniated mercury ointment was promptly alleviated by injection of BAL by William and Beach (J 14 1?90, 1950). Metaphen (Belote and Marshall: JMichSMS 34 1–, 1935) Merthiolate (Hill JAllergy 19: 1–, 1947) and Hydrophen, containing phenyl mercuric nitrate which is highly germicidal (Wilson: NebrSMJ ?4: 0, 1939) are all of them hazardous (Gall and Underwood J 140 ?90, 1949). Mercury amalgam fillings have been reported to cause perioral dermatitis (Traub and Holmes: ADS 38: 349 1938; Robinson and Bereston ADS 59: 116 1949). A sailor tattooed with cinnabar developed a severe allergic rash (Novy ADS 49 172 1944).

OINTMENT BASES, innocuous as they may seem, are not wholly to be trusted, by any means. Even petrolatum may irritate (Hollander ADS 39 49 1939). Vesiculation from contact with petrolatum was observed by Rosenbaum (ADS 48: 193, 1943) but patch tests with it are rarely positive (Levin and Moss: AnnAllergy 6: 5?9 1948). Sometimes when a bland ointment appears to irritate the fact is that it covers over pathogenic organisms and allows them to thrive. Among patients intolerant of Aquaphor cholesterol was the offending ingredient in 8 of the 9 (Ellis: ADS 56: 801 194). While lanolin is rarely irritating, the allergens in its composition seem to be the mixed alcohols rather than the fatty acids (Sulzberger and Lazar: JID 15 453, 1950). The specific excitant fraction of lanolin was shown in one allergic patient to be a yellow glassy solid which after acetylation was no longer irritant (Everall and Truter: JID 22: 493, 1954).

Olive oil is not a good vehicle for other ingredients of a topical application, probably because of the unsaturated fatty constituents which, when percutaneously absorbed, incite an inflammatory metabolic process (Sutton: J 122 34 1943).

OPIUM derivatives may cause contact dermatitis, especially on the hands of nurses and pharmacists (Jordan and Osborne: J 113: 1955 1939). Rashes on eyelids, neck and hands of workers in a morphine factory were observed by Dore and Thomas (BJD 56 177 1944) and Green (ib p. 18?). The once popular lead and opium lotion is honored only by time.

SULFONAMIDES are notorious for their capacity to sensitize when applied to the skin, especially in the presence of pathogenic staphylococci and when coincidentally given by mouth. See Fowlkes et al. (SouthMJ 35: 1018, 194–). Livengood and Pillsbury (J 121 400, 1943). Weiner (ib., p. 411). Park (BMJ 69 1943). Tait and Klorfain (Lancet I 39 1944). Sulfathiazole 5% ointment sensitized 1– of 18 patients of Darke (J 1 4 403 1944). Such sensitization introduces widely various hazards from sulfonamide derivatives, lacquers and plastics which the patient may subsequently meet nonmedicinally. There exists little excuse to use sulfonamides topically said Lane (SouthMJ 38 125, 1945) in describing 1– illustrative cases including one death; there exists not any excuse I would say now.

VITAMINS may irritate the skin: nicotinic acid caused redness and itching of some of the personnel engaged in its manufacture (Watrous J IL –13?, 1939); synthetic vitamin K in 1% concentration is a primary irritant and the crystals will ulcerate the skin (Page and Bercovitz AmJMSc ?03: 566 194–); and biotin concentrate irritated the hands and arms of a laboratory worker (Keller JAllergy 14 8? 194–).

MEDICINAL CONTACT DERMATITIS MISCELLANEOUS MEDICINES

Acriflavine dermatitis (Beare Lancet 1 410, 1947)
Antistine eye drops (Mosko and Peterson JID 14 1, 1950)
Atabrine (Andrews ADS 50 140, 1944)
Antiseptic baby oil (Lapin AmJDisChild 62 ?? 1942)
BAL (Cornbleet JID 8 ?31 1947)
Benzoin (Steiner and Leifer JID 13 351 1949)
Chlorpromazine (Thorazine) disabling contactant in 2 nurses (Lewis and Sawicky J 157 909 1955)
Coal tar (Simon and Brandt ADS 68 584, 1953)
Codeine (Palmer ADS 46 ?2, 1942) contact with cough syrup, case
Corticotropin from pork but not from beef (Zeligman J 149 262, 1952)
Emetine in persons who filled ampoules (Kile and Welsh ADS 45 ?30, 1942)
Ephedrine (Carpenter ADS 34 1038 1936. Lewis ADS 49 379, 1944. Spencer ADS 51 48, 1945) nose drops

Formaldehyde (Rostenberg et al.: JID 19 459 1952) quite specific, reaction sometimes delayed 72 hours.

Furacin (Richter and Mocchio: NYSJM 49 2325, 1949 Fox: ADS 63: 378, 1951; Morin: J 133: 942, 1947 George: J 156: 247 1954)

Hexylresorcinol (Templeton and Lunsford: ADS 25: 439 1932) in toothpaste; Cummer (J 100 384 1933), Walter (J 104: 1807 1935)

Iodoacetic acid, a violent corrosive (Marcus and Frerich J 14 : 895, 1950)

Isonicotinic acid (Jordon J 149 1316, 1952)

Lanolin (Lilingood et al. J 148: 334 1952) trouble with ointment bases (q.v.)

Phenol-camphor once popular treating tinea (Hubler J 123: 990, 1943; Ronchese: RhodeIslMJ 25: 176 1942)

Phenolphthalein (Skinner ADS 59 338 1949)

Physostigmine in eye drops (Alden and Jones: ADS 37 82, 1938)

Quotane (Daly ADS 66: 393, 1952)

Resorcinol (J 121: 985, 1943)

Salumiek (Sheard: ADS 70: 115, 1954)

Metals.—Many different metals are concerned with contact dermatitis in ordinary as well as occupational life.

Aluminum does not irritate but dermatitis attributed to it is generally caused by oils or cleansers. Arsenic from insecticide dust contaminating the clothing may cause erythema and vesiculation (Monahan JMoMS 41 54 1944) Cobalt, contacted by workers making cutting tools (carballoy) was recognized as a contactant irritant by Schwartz et al (JAllergy 16 51, 1945) It has induced rashes resembling pityriasis rosea and also asthma Conjunctivitis and upper respiratory irritation caused by vanadium was reported by Symanski (abs J 113 1080 1939) Selenium caused purpuric contact dermatitis according to Pringle (BJD 54 54 1942)

Antimony vapors induced itchy varicelliform eruptions in exposed workers (Fell PresseM 47 1133 1939)

Beryllium may produce severe papulovesicular and ulcerative dermatitides (Van Ordstrand et al. J 129 1084, 1945) and conjunctivitis (Edit BMJ 2 231 1946) Discrete papular lesions, papulovesicular lesions and ulcers were observed among workers in beryllium production plants by DeNardi et al (OhioSMJ 45 567 1949) A sarcoidal foreign body granuloma (q v) results from intracutaneous reaction to beryllium compounds such as the phosphores of fluorescent lamps, and pneumonitis resembling that from silica is caused by their inhalation (Grier et al. JIndustHyg 30 228 1948) Acute eczematous contact dermatitis is the usual type of intolerance, appearing in from 7 to 14 days after exposure and disappearing in a few days after removal from contact but chronic cases also occur often in the form of ulcers over the knuckles, sluggish unless curettage or excision is performed (Van Ordstrand AnnIntMed 35 1203 1951) A chronic beryllium ulcer may develop at the site of an injury from a broken fluorescent light bulb curable by excision. See Beerman (AmJMedSci 221 462, 1951) review

Chromium is at fault in many cases of persistent and rebellious allergic dermatitis. Chromate and dichromate may touch the population at large as well as industrial workers, being met with in tanning photoengraving the plating of various objects including automobile and kitchen trim, paint, antirust compounds and cement (J 119 851 1942 Pirila and Kilpio abs YBD 1949 p 152 Vaccaro IndustM 10 246 1941) Zinc chromate primer caused nummular eczema of hands and forearms of aircraft workers who did not harden, noted Hall (J 125 179 1944) A droplet of chromic acid produces painless dry gangrene which heals with scar The nasal septum is likely to suffer perforation in chrome workers. The caustic action is not associated with sensitization (Edmundson JID 17 17 1951) Diesel locomotive radiator fluid and fuel may contain antirust compounds and so incite chrome dermatitis (Winston and Walsh J 147 1133 1951) BAL used topically in 3% concentration was helpful in chrome dermatitis reported Cole (ADS 67 30 1953)

Lithium, like sodium produces alkali burns (QMN J 126 268 1944)

Nickel is a common cause of contact dermatitis. This metal may reach the skin by way of coins, spectacle frames, zippers, pins, garter fasteners, jewelry and the like (Foster and Ball ADS 31 461 1935 Downing ADS 41 568 1940) Plated articles as well as alloys may be the source. Although

the cutis appears to be the shock tissue passive transfer experiments in 11 cases were not successful (Cormia and Stewart CanadMAJ 32 270 1935) It seems that sweat serves to ionize the metal (Taylor et al. BMJ 2 40 1945) When 54 patients known to have been nickel sensitive were traced after various prolonged lapses of time by Morgan (BJD 65 84 1953) 43% of them had become negative to patch testing and some of these still had eczematoid dermatitis despite their negative tests to nickel *Many however remained* reactive one patient retaining nickel allergy for 11 years.

Platinum salts, dissolved in water and contacting laboratory and refinery workers via liquid sprays and splashes caused severe dermatitis and/or asthma reported Roberts (ArchIndustM 4 549 1951) The onset was sometimes gradual until an acute attack developed. The lesions were urticarial in acute stages, eczematous in chronic Scratch tests were positive in the asthmatic ones, and chest x rays sometimes showed low grade pulmonary fibrosis.

In a valuable and original study of 34 cases of nickel dermatitis, Epstein (Trans ADA, 1955) found 22 reactive to both patch and intradermal tests, 5 reactive to patch tests only 6 reactive to intradermal tests only and 1 negative to both types of tests. Cross sensitivity between Ni and Co *was present in 11 of 28 tested fewer showed Ni-CO or Ni-Cr cross sensi*tivity It was apparent that the epidermis is not exclusively the shock tissue in contact dermatitis, but that the dermis often is (see Contact dermatitis, pathology)

See Sully (Chromium, Academic Press, 1954) sources, alloys metallergy technology of chromium Walsh (J 153 1305 1953) chromat hazard l industry only the hexa valent compounds sensitize, Denton et al (JID 23 189 1954) Cr in cement, Hilt (*Dermatologica* 109 141, 1954), Cr found in surprising places, including laundry work Haxthausen (abs YBD *1954 p 420) Cr not specifically bound or retained but disappeared in 24 h in allergic and* normal animals, Gaul (AnnAllergy 121 429 1954) of 40 cases of dermatitis of hands, 18 reacted to metal, 12 of these to Cr

Oils used in lubrication and cutting with machine tools provoke folliculitis with acneic comedones pustules and scarring The parts affected are especially the hairy forearms and thighs. Prevention can be successful if efficient effort is made to minimize the exposure to oil if the skin is thoroughly *cleansed after exposure and if the clothing is* kept properly clean; no local therapy is necessary ordinarily (Schwartz PHRpts 56 1947 1941) The insoluble cutting oils are the worst offenders (Peck J 125 190 1944)

The addition of antiseptics to cutting oils is unnecessary and objectionable The bad odor oils develop is due to chemical changes induced by heat not by fermentation and an antiseptic is likely to be an irritant or a sensitizer itself *Low melting point and unsaturated oils are more irritating than high* melting point and saturated oils (Klauder and Brill *ADS 56 197 1947)* Oil acne of the forehead and face may be caused by hair oil such as Brilliantine (Garnier abs YBD 1946 p 277) Dermatitis of the face in certain workers near ventilator openings was found to be due to a petroleum solvent conveyed by air currents (Campbell and Schwartz OccupM 3 570 1947) See Council on Industrial Health Rpt. (J 157 1611 1955) industrial oils, composition of cutting oils, and dermatoses caused thereby

Chlorinated oils especially the dielectric chloronaphthalenes, may induce acne of extreme severity including comedones, milia, and sebaceous cysts, along with the inflammatory lesions subsequent to them Hot chlorine compounds and fumes are the active agents rather than cold wax (Jones JIndust Hyg 23 290 1941) Such acne has been named according to the product in the manufacture of which it was observed, as perna krankheit ' halowax acne, cable rash (Sulzberger et al. NYSJM 34 899 1934) All persons exposed to chloronaphthalenes chlorodiphenyls, or chlorodiphenyloxides will develop acne within a few months unless stringent precautions are used (Schwartz and Peck NYSJM 43 1711 1943) The face is exposed and the thigh, groin and umbilical regions are affected via soiled garments. Coal tar workers are subject to oil acne too but to a less degree than workers with

heavy tar distillates and pitch. A person with seborrhea prone to develop acne should not be hired for such work. Acute yellow atrophy as well as mere dermatitis may be caused by chlorinated naphthalenes (Collier Lancet 1 72, 1943) Good and Pensky (ADS 48 251 1943) described erythematous and vesicular dermatitis too and noted concomitant complaints of lassitude anorexia impotence headache alopecia, and loss of weight in their patients. Patch tests are negative Chlorophenate moth proofing in fabrics may cause oil acne

Almost every sebaceous gland had become a milium, sebaceous cyst or acne pustule in a man I saw who was exposed to a chlorinated refrigerant His disease did not yield until large doses of estrogenic substance were given. Premarin 1.25 mg daily appeared to exert a conspicuously beneficial influence on his sebaceous gland hypertrophy

See Leo Butler (ADS 36, 251 1937) Nakauchi (bs ADS 46 292, 1942) histology of lesions in rabbits Schwartz (J 122 158, 1943), Morri and Tabershaw (J 121 192, 1943) Meigs et al (J 154: 1417 1954) chloracne of face from prolonged exposure to low concentration of chlorinated diphenyl.

Tar acne is not different from the acneiform folliculitis caused by other oils and chlorinated waxes. It is seen in hemp workers, flax doffers and those who come in contact with the distillates of coal and residues of gas (Ormsby Dis. Skin, Lea & Febiger, 1937 p 1200); Jones and Alden ADS 33 1022, 1936) See also Photosensitization.



Fig. 121—Acneiform folliculitis from cutting oil. (Dr Clyde L. Cummer)

Keratosis follicularis epidemica appeared in patients handling wax covered tinfoil reported by Schenker (Dermatologica 97 35 1948)

PHOTOSENSITIZATION BY CONTACTANTS (BERLOCQUE DERMATITIS) —Pigmentation results from the application to the skin of toilet waters containing oil of bergamot (from the juice of Persian limes) or some other essential oils, followed by sunlight or quartz light. The lesions appear as dark red areas changing to brown slightly mottled with red. Certain grasses may by their oils so sensitize the skin that dermatitis and pigmentation of striking linear and crisscross configuration follow contact with them when sunshine is superadded. *Dermatitis bullosa striata pratensis* was the mellifluous name of Oppenheim (AnndeD 3 1 1932 ADS 46 541 1942 see Sandler J 112 2411 1939) Covered areas although contaminated with the essential oils are not affected. The furocoumarines of plant juices are responsible for this abnormal responsiveness to light of from 3100 to 3700 A While the furocoumarines vary in activity as photosensitizers, there is no known correlation between their chemical structures and their sensitizing powers (Kuske AfDuS 178 112, 1938 abs YBD 1939 p 568 1941 p 85) Parsnip (Jensen and Hansen ADS 40 566 1939) lime oil (Sams ADS 44 571 1941) and agrimony (O Donovan BJD 54 39 1942) have been carefully studied, but the photocatalysis of pigment remains ill understood. Tar and pitch handlers may develop melanosis as an occupational photosensitization phenomenon (Foerster and Schwartz ADS 39 955 1939)

Differing from the usual type of photosensitization a phenomenon was described by Sams (Trans ADA 19 ..) in which papular and papulo-urticarial lesions appeared diffusely in an area where a digallol trioleate sunscreen had been applied not in areas of unprotected sunburn Patch tests with this mixture of tannic acid derivatives was positive only after exposure to ultra violet light



Fig. 124—Contact photosensitization from a toilet water (Simons YBD 1939 p 125.)

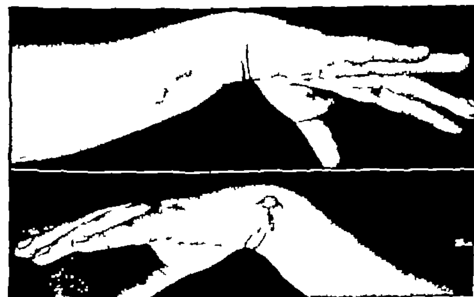


Fig 125—Contact photosensitization from Persian lime. (Gross ADS 63 370 1951)

See Cummer and Dexter (J 109 495, 1937) Klaber (BJD 54 193 1942) Bellringer (BMJ 1 984, 1949) Belisario (AustralJD 1 132, 1952) cases, from parsnip peeling resembling mustard gas dermatitis Raegö and Dolmay (DWchn 130 1150 1954) Rut graveolens source of rutin, causing bullous occupational dermatitis requiring sunshine, moisture and contact with fresh leaves or pollen

Plant and Weed Dermatitis.—Plants are among the commonest causes of contact dermatitis. Poison ivy primrose and ragweed are noteworthy of

fenders The major skin sensitizers among the flowers and shrubs according to Shelmire (SouthMJ 33 337 1940) are primrose painted daisies (pyrethrums) and feverfew and other members of the chrysanthemum family

Woodworkers, carpenters, florists, farmers, agriculturists in various kinds of work and food handlers (q v) are obviously subject to exposure but products of vegetational life are handled by all people One cannot overlook such a seemingly obscure contactant as cocobolo wood which provides handles of knives and mouthpieces of musical instruments (Leider and Schwartzveld ADS 62 125 1950)—examples are endless.

Algae blue-green (Cohen and Reif: JAllergy 24: 452 1953)
Brazil nut in candy fa tory (Markson ADS 46: 831 194_)
Carrot in canneries (Peck et al.: ADS 49: 266 1944)
Celery in farming industry (Wiswell et al. JAllergy 10: 306 1949)
Clematis, cau ing recurri g summer eruption of exposed parts (Lancaster SouthMJ 30: 707 1937)
Figs including photosen itization (Behcet et al.: AnnDeD 10: 22, 1949) Burning off wild fig ca sed dermatiti and blistering nasopharyngitis (Engli h and Grey: MJAustral 1: 5 8 1943)
Hops (Cookson and Lawton: BMJ _: 376 1953)
Krameria (Grolnick: JID 1: 179 1938)
Lemon grass oil, common in essential oils (Mendelsohn: ADS 33: 94 1946)
Mango from Anacardi ceae; can cause sores in and about mouth (Kirby-Smith: AmJTropM 19: 373, 1939; Zakon: J 113: 1509, 1939; Goldberg: J 156: 9 4 1954 perioral from peel not pulp)
Onion and garlic, in a cook (Burgess: CanadMAJ 66: 275, 195_)
Orris pollen, and root from hizome of iris, useful to hold perfumes (Prickman : PSMMC 9: 291 1934)
Parsnip, see Photosensitization
Primrose (Low: BJD 36: 292, 1924)
Tobacco, reagins a d vascular disease (Harkavy: JID 2: 247 1939); arsenic spray (Barksdale: J 115: 67 1940)
Tulips, paronychia in sorters and packers of bulbs (Overton: Lancet : 1003, 1970); barbs of testa traumatize, and sugar in juice ferments (Bertwhistle: BMJ 1: 1133, 1936); positive patch tests (Caulfeld CanadMAJ 34: 506, 1936)
Wood, cocobolo (Howell and Ballr: ADS 62: 400 1950); manzanillo or beach apple latex blisters may damage cornea (Snow and Harley ADS 49: 226, 1944); tropical wood (Piorkowski: EAfrMJ 21: 60, 1944); mesquite (Fox: ADS 44: 1009, 1941); walnut juice (Siegel: ADS 70 511 1954)

Articles containing lists of plants t which llergy has been observed include Harville (JAllergy 4 537 1933), Bonen (J 101: 1527, 1933) wood Shelmire and Black (J 108 719 1937) Shelmire (SouthMJ 33 337 1940) Allen (AmJTropM 23 3, 1943) Panama plants Weber (ADS 67: 388, 1953) sawdust.

See also Photosensitization by contactants

CASHEW —*Anacard um occidentale* a nut-bearing evergreen tree of a genus which includes poison ivy mango a d pist cia, i the source of an oil obtained from the nutshells which has many uses and i also a potent sensitizer if its irritant property is not destroyed by heat (Downing a d Gurney: JIndustHyg 22: 169 1940) Contact dermatitis does not follow from ingestion of cooked nuts. Th resins from cashew re of the phe ol-formaldehyde type, useful in mucilage, varnish, printer's ink and the like (Schwartz et al. IndustM 14: 500 1945) See Tulipan (Ind stM 5: 626, 1936) While some workers harden others do not Anacardol, a primary irritant in adequate concentration, i related to urushiol, so that cross sensitivity to poison ivy i common according to Schwartz.

DHOBIE MARK DERMATITIS i the contact dermatiti provoked by the laundry marking material derived from the ral or bella gutti in I dia (Livingood et al. J 123: 23 1943) This pote t sensitizing substa ce i not destroyed by boiling. The disease was long confused with dermatomycosis. The marking nut tree is a member of th Anacardiaceae and its tar or oil i a blistering primary irrit nt. A bottle of thi was broke in the mail and injured the ski s of several postal workers (Goldsmith J 123 27 1943) See Merrill (J 124: 222, 1944)

POISON IVY —Dermatitis results from contact with the oleoresin which may be conveyed indirectly as well as immediately Vesicle fluid and smoke from the burning plant are not noxious (Howell ADS 50 306 1944 Pratt and Corson ib 51 316 1945) Human beings are not born allergic to the oleoresin, but acquire sensitivity Guinea pigs can be sensitized by application or injection of the antigen (Ginsberg et al. ADS 36 1165 1937) The antigen is a primary irritant when it touches the skin in sufficient concentration, and it adheres strongly to the epidermis yet may be present in such quan

tity as to be spread about from the initial site of contact by way of the fingers or clothing. The initial attack of ivy dermatitis which sensitizes differs from subsequent attacks occurring after sensitization exists. The first attack is likely to manifest itself as an impetiginoid exudative painful lesion from primary irritation, a lesion sterile on culture which rebels at all kinds of treatment and remains practically unchanging for several days. Then sensitization, having developed, makes itself evident with swelling, spreading vesiculation and the appearance of distant lesions where relatively low concentrations of antigen reached the skin, low enough not to serve as primary irritants but

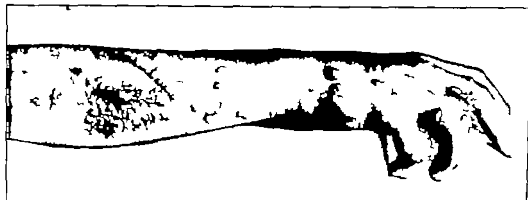


Fig. 126.—Dermatitis venenata, due to *Rhus toxicodendron*. (Dr. Howard Fox.)



Fig. 127.—Poison ivy dermatitis, not as yet vesicular. (Dr. J. P. Gueguierre.)
Fig. 128.—Poison ivy dermatitis at the height of reaction, the fifth day of the eruption.

ample to evoke reaction after allergy has incubated. Thereafter the individual is allergic and the next time even a little antigen reaches his skin, he reacts after a period of some 36 hours, with typical allergic vigor. From the time such a flare appears until it reaches its height is a period of about 5 days during which a patient may expect to get worse. More or less abruptly in the uncomplicated case improvement takes place, the disease "breaks," and the patient, miserable as he has been, knows that he is making the change for the better. About three weeks more are then required for the skin to revert to normal.

While the adherence of antigen to the epidermis is firm nevertheless some of it can be picked up by any oily topical application which will smear disease to previously unaffected parts. It is an error to apply any kind of ointment during the early stages of poison ivy dermatitis.

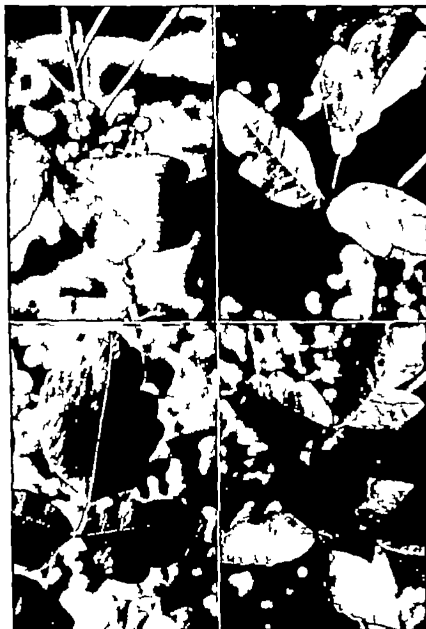


Fig 129 —Poison i y (From W T V ughan and J H Black Practice of Allergy Mosby ed 2, 1948)

Hydrourushiol, a stable crystalline substance to which all are sensitive who are sensitive to poison ivy was synthesized by Mason (JAmChemSoc 67 1538 1945) and quantitatively standardized patch tests were designed by Dunn et al (JID 6 323 1945) Not all human beings exposed to a strong extract of poison ivy develop sensitivity (Simon and Lotspeich JID 2 143 1939) and it is said that individuals with atopic dermatitis cannot be

sensitized If the skin is painted with the extract and then after 12 hours is extirpated, *generalized sensitivity nevertheless develops.* *To prevent systemic* absorption and reaction circumvallation of the painted island must be prompt and must go through to muscle so as to interrupt lymphatic absorption (Landsteiner and Chase JExpM 69 767 1939)

Poison ivy oak, and other variants represent a single polymorphic species with habitat variations (Shelmire JID 4 337 1941)

Many individuals are sensitive both to poison ivy and cashew nut shell liquid (Keil et al. Sc 102 279 1945)

Severe reactions may follow the use of poison ivy antigen, and large or frequent doses may prove dangerous, though French and Halpin (AnnAllergy 1 131 1943) were among those who believed that injections of an alcoholic extract helped their patients. The Council on Pharmacy (J 127 912, 1945) stated that treatment of the acute disease with ivy extract should be discouraged because many patients are made worse and no proof exists that any are helped. Many times I have observed the ill effects (see Goldman Ohio SMJ 38 146 1942) Prophylaxis by antigen injections is of extremely doubtful value (Sompayrac AmJMSc 195 361 1938), a statement true of all kinds of dermatitis venenata, and may cause a violent outbreak. Used in treatment injections caused two cases of acute glomerulonephritis, one of them fatal reported by Shaffer et al (J 146 1570 1951) Four patients with resultant exfoliative dermatitis were presented by Reyer (AnnAllergy 11 91 1953)

Oral desensitization may perhaps be partially successful but antigen must be given by mouth over a long period of time in doses large enough to cause gastrointestinal upset and pruritus ani (Shelmire ADS 44 983 1941) The oral tincture poisoned one patient, causing convulsions and yielding no hyposensitization (Lowenburg J 135 91 1947) Large doses by mouth have not damaged the kidneys in the human, and a rabbit killed with ivy extract showed no kidney damage, reported Howell et al (ADS 70 426 1954)

Hope of the future development of successful parenteral hyposensitization may be seen in the fact that some resistance to subsequent sensitization by hydrourushiol developed following injection into guinea pigs of a hydrourushiol albumin conjugate in experiments by Mason and Lada (JID 22 457 1954)

There is one way and one way only to keep from having ivy dermatitis, and that is to remain out of contact with the stuff

Patients poisoned severely enough by poison ivy to require hospital care were studied by Templeton et al. (JID 8 53 1947) Some developed a temperature of 101° Leukocytosis averaged about 10 000 to 12,000 but reached 16 000 in one case Eosinophilia averaged about 5 to 10% but reached as high as 20% The urine remained normal in these cases.

In the treatment of ivy poisoning the natural course of the disease should be kept in mind. Following contact, there is a latent period of about 36 hours in the allergic patient after which dermatitis starts. Erythema and local swelling of the initial lesions is followed by vesiculation and diffuse swelling with erythema, paroxysmal severe itching and more or less intoxication, reaching a peak on about the fifth day During the first day or two of the rash the patient tolerates his suffering as a rule. When he seeks help he has missed perhaps two nights of sleep and is within 48 hours of the acme of his disease He seeks help at a time when the practitioner needs only to temporize for 2 or 3 days to reach the breaking point of the disease The speed of recovery is not accelerated by any agent applied to the skin (Hoagland et al. J 146 612, 1951)

Treatment therefore is aimed at ameliorating symptoms. Cool showers are comforting and do not spread the antigen although of course the violently irritated skin will not tolerate soap Baths in aluminum acetate a tablespoon

to the tub of cool water are helpful, and soaks in potassium permanganate 5 grains to the gallon. Sedation with aspirin, chloral hydrate phenobarbital or opiates, if needed, should not be withheld. A child in the summertime suffering from not too much dermatitis will enjoy an air-conditioned movie and so pass away several hours of the time required for the skin reaction to complete itself Ointments of all kinds are wrong Antihistamines topically are worthless or injurious in my opinion by mouth they may reduce distress to some extent, Benadryl having a useful sedative effect as well as antiallergic. Phenolated calamine lotion and cold moist poultices are commendable. One may scrub the blisters with gauze wet with alcohol then apply 10% tannic acid for 20 to 30 minutes, repeating these measures as new blisters form with excellent relief though the face may not be so treated, according to Schwartz and Warren (PHRpts 56 1039 1941) although this is not my own recommendation.

For a small area the application of flexible collodion may give comfort (Woodward J 114 2587 1940) but it may also allow secondary infection to luxuriate A paint containing coal tar 10 benzine 20 and acetone 70 was favored by Tulipan. The only treatment appearing to promise actual neutralization of the poison on the skin utilizes the hydrous oxide or carbonate of zirconium which in vitro combines with the hydroxyl groups of urushiol to render it inactive (Cronk and Naumann JLabClinM 37 909 1951) Non toxic on topical application, the chemical in 5% concentration reduced the reaction to patch tests and effected apparently conspicuous benefit in 85% of the patients with ivy poisoning (Cronk ADS 66 282 1952 Strauss and Bruck JID 20 411 1953) The commercial preparation available in 1953 was worthless.

Cortisone and ACTH have been advocated and sometimes apparently help considerably (Falk et al. JID 18 307 1952 Gay and Murgatroid JAllergy 23 215 1952) Fuhrman (JMoMA 51 113 1954) obtained good palliative effects with ACTH and my experience is corroborative

Prevention by use of 10% sodium perborate in a protective ointment base is said to succeed (Schwartz et al.: PHRpts 57 578 1942) Soap will remove only some of the antigen if it is used within 5 minutes of exposure, and saturated aqueous $KMnO_4$ may partially neutralize within 15 minutes, but no effective prophylactic exists believed Howell (ADS 48 373 1943) A vanishing cream freshly prepared containing 2% potassium periodate may serve as a preventative (Schwartz Sci 92 6 1940) Control measures were studied by Goldman (OhioSMJ 40 629 1944) who recommended efforts to eliminate the plant itself, to prevent contact of people with the plant and to render the individuals less susceptible by means of oral hyposensitization.

Ragweed Dermatitis occurs in adults rarely in children. Its features are characteristic the seasonal incidence, annually repeated, during July and August and maximally in September disappearing with the first frost the redness, swelling and itching of the eyelids and inflammation of the exposed surfaces, especially the hands, wrists, ankles and face the exacerbations which occur after hunting weeding or otherwise contacting the plant and the local reaction with distant flare on patch testing The dust of ragweed in grain and flour may serve as an industrial hazard (Jordan et al. ADS 46 721 1942)

Hyposensitization by oral administration of the specific oleoresin is said to be practicable (see J 123 733 1943) It helped some of the patients of Fisher (JID 19 271 1952) all of whose 18 patients reacted positively also to pyrethrum. One may advise people who are severely afflicted to move to a location where ragweed does not grow (Slater et al. OccupatM 2 298 1946)

Eczematous reactivity is caused by the oil, which does not induce an urticarial reaction. Reactivity could not be passively transferred in experiments of Pascher and Sulzberger (ADS 28 223 1933) See Brunsting et

al (J 103 1285 1934 106 1533 1936) Oral desensitization was claimed to be curative in the case of Fisher (ADS 68 592 1953) the patch test reaction underwent reversal Cortisone and ACTH help very little

WEED DERMATITIS was reviewed by Shelmire (J 113 1085 1939) During the first few years the dermatitis is seasonal corresponding closely to the growing season of plants. At the onset the eruption is usually erythematous, scaling and pruritic Exacerbations caused by massive exposures are characterized by increase in erythema swelling and oozing and occasionally by fine vesiculation With seasonal recurrence dermatitis becomes more widespread, owing to increase in sensitivity and manual spread of antigenic oleoresins to areas of the body covered by clothing Thickening of affected areas follows trauma occasioned by protracted scratching and rubbing Seasonal attacks extend further into the winter before completely healing Sooner or later the eruption becomes perennial—extremely *severe during the growing season of* plants with remissions during the winter months. Erythema edema oozing and crusting disappear but pruritic lichenified areas often persist until the new spring weeds return. The sites affected are usually the exposed areas such as the face neck backs of the hands wrists and ankles. The eruption *gradually spreads to involve the forearms and legs. In men the penis and the* anterior surface of the scrotum are often erythematous and thickened. Occasionally patchy areas of dermatitis appear over the trunk and groins. In



Fig 136—Ragweed dermatitis (Sutton J 73 1433 1919)

the more widespread and long-standing cases those areas which are more easily irritated by external agents, such as the face the sides and front of the neck and the flexures, become markedly lichenified. Prolonged healing time is characteristic If patients with weed eczema are hospitalized and contact with vegetation is absolutely avoided disappearance of the eruption usually occurs within from 3 to 6 weeks. If these patients are ambulatory but avoid actual contact with weeds the healing time is frequently prolonged for from 6 weeks to several months, since they continue to come in contact with small amounts of the antigenic oleoresins through contaminated work clothes, tools, pets, udders of cows. Most of the affected persons are farmers and others whose occupations bring them into almost daily contact with vegetation. Each weed contains an ether-soluble, oleoresinous dermatitis-producing fraction and a water-soluble albuminous, hay fever producing fraction. This can be demonstrated by tests on a person in whom dermatitis develops from contact with a specific weed and hay fever or asthma from inhaling its pollen. Patch tests on this person with portions of the antigenic plant will evoke a delayed eczematous reaction If all the dermatitis-producing oleoresin is removed by repeated ether extraction the remaining de-oiled residue which still contains the atopic fraction will then evoke the typical immediate urticarial scratch or intradermal hay fever reaction. Eczema producing oleoresins appear on the leaves stems, and flowers of many weeds as tiny globules of oil,

readily seen with a hand lens. These oleoresins are sticky and adhere tenaciously to the skin or clothing. Contact of sensitized persons directly with the plant or with contaminated intermediary objects is followed by dermatitis. Previous contact is necessary for the development of sensitization to a plant. When weed-sensitive persons were tested on unbroken areas of the skin by the uncovered method many developed an apparent flare-up of the eruption. Focal flare-ups did *not* occur when the same persons were retested and the patch sites were completely covered to prevent manual transference of the oleoresin. All attempts to demonstrate antibodies in blood serums of weed sensitive persons by the Prausnitz Küstner method of passive transfer have failed.

Rubber Dermatitis is commonly due to sulfur monochloride used in the curing process. It can be rendered nonirritant by treatment with an alkali such as 4 per cent sodium hydroxide solution. An accelerator such as paranitrosodimethylaniline may be the irritant (QMN J 113 1245 1939). Mercaptobenzothiazol caused most of the trouble studied by Bonnevie and Marcussen (ActaD-V 25 163 1944). *Rubber and rubber cement are used in shoes,* and may cause dermatitis of the feet (Anderson CalWM 61 65 1944).

An antioxidant in rubber gloves caused depigmentation, but repigmentation eventually occurred when contact had been interrupted (Oliver et al. ADS 42 993 1940). The antioxidant was Agerite alba the monobenzyl ether *of hydroquinone. I saw a Negro physician with a startling white cross on* his back caused by his suspenders. See Zakon and Goldberg (ADS 64 441 1951) on occupational leukoderma; see also Melanotic hypopigmentation; Chloasma treatment.

Rubber gloves may cause troubles for surgeons or housewives. Beneath a *glove* the skin is moist and warm so that bacteria thrive while of course allergy to constituents of the gloves may produce dermatitis. Neoprene gloves (Stanzoil) big and loose using cornstarch on the hands to aid in getting the gloves on, are what I prescribe for protection of housewives. I do not consider the cloth lined gloves so satisfactory. The irritants in rubber gloves are usually sulfur accelerators, antioxidants, plasticizers or dyes (Sidi and Hincky PresseM 62 1305 1954).

See QMN (J 143 1298, 1950) Burgess (CanadMAJ 45 222, 1941). A review of 124 cases of rubber sensitivity was given by Leider et al. (ADS 65 557 1952). Miscellaneous rubber irritations have been reported: rubber adhesives (Blank and Miller J 149 1371 1952) condoms (Ratner J 104 1189 1935) and Clarke (JID 10 47, 1948), spongy powder puffs (Hollander J 113 2271, 1940) eyelash curlers (Curtis ADS 62 282, 1948) gas masks (Petro BMJ 1 631 1942); dress shield (Shepherd and Krall JIndustHyg 2 32, 1920) rubber bands (Morris J 152 1218 1953) a tourniquet of orange colored rubber containing thiobetanaphthol (Schamberg and Flesch JID 21 59 1953).

Irritants met in the manufacture of synthetic rubber and protective and preventive methods were described by Schwartz (J 127 389 1945).

Hair loss due to volatile intermediary polymers of chloroprene was studied by Flesch and Goldstone (Sci 113 126 1951). *Application of such compounds to the skin of experimental animals* produced complete hair loss, with disappearance of follicles and sebaceous glands, in 10 days, the changes disappearing spontaneously in 6 weeks. See Depilation, experimental.

Soaps are alkaline to a greater or lesser degree and are defatting agents, lacking which capacity they could not cleanse. Skins are variable with respect to the amount of soap usage they can withstand. Hands that may tolerate soap twenty times a day in the warm summertime may tolerate only half a dozen washings in winter when the air is dry the skin cool and the sweat and sebaceous secretions diminished. Soaps and detergents are frequently the inciting cause of dermatitis of the hands, the disrupted epidermis then allowing bacterial invasion (Jordon et al J 115 1001 1940).

A technic for comparing the effect of soaps and detergents on the hands of housewives was elaborated by Johnson et al (ADS 68 643, 1953). A skin already inflamed tolerates soap poorly (Goldman J 109 1317 1937). Any soap contains many ingredients, each one of which embodies the modicum of irritant or sensitizing hazard. Tests of the mildness of soaps were discussed by Jordon et al (NYSJM 36 791, 1936) and Kooyman and Snyder (ADS 46 846 194). Many a patient imagines that water alone is the cause of her soap troubles. I counter the argument with a statement of the fact that about three-quarters of a human body is water and a person intolerant of water would indeed be in trouble.

Synthetic Resins were described by Schwartz (JID 6 279 1945) with respect to their manufacture and use hazards and dermatologic connotations. They are irritating in inverse proportion with the completeness of their polymerization. Fully polymerized they are glasslike and inert but in that stage lack the flexibility and adhesive qualities for which they are likely to be designed. The monomers are usually primary irritants.

The principal types are: (1) phenol formaldehyde (furfural phenol formaldehyde, lignin formaldehyde, cashew nut shell liquid formaldehyde; (2) urea aldehyde; (3) an aldehyde condensation series using of simpler chemicals, urea and formaldehyde including sulfonamide resin and melamine; (4) ester gum made of glycerols or glycol with natural resin; (5) alkyd resins, made of glycerols or glycol with polybasic acid or anhydrides such as phthalic or maleic usually used as coatings, the cure completed by drying; (6) modified alkyd combining alkyd resins with Styrene vinyl chloride allyl alcohol or another resin; ( ) polyvinyl resins; (8) acrylate and methacrylates; (9) polystyrene; (10) allyl alcohol and allyl modified alkyd (11) cumarone and indene, made from tar residue; (1) cellulose nitrate and acetate; (13) mixed resins, combining two or more of the preceding; (14) polymerized hexamethylene adipate (Nylon); (15) chlorinated resins, from chlorination of oil balsams and waxes, (16) rubber hydrochloride (Pliofilm). The solid resins are used for making plastic panels knobs, buttons, ornaments bottle caps, dishes, vessels, dentures, garments, gears rubber compounds, adhesive plaster etc. The semisolid resins are used for glues, fillings, adhesives, etc. Solutions of the resins are used for lacquers, varnishes, floor finishes fabric finishes, hair lacquers, etc.

See Lockey (JAllergy 15 198, 1944) Sulzberger (ADS 41 216, 1940) lacquer on bracelet Schwartz et al. (J 115 440 1940) resin lining of cans, Nelson and Fletcher (ADS 44 213, 1941) underwear fabric finish Markuson et al. (IndM 12 383, 1943) resin formol dermatitis QMN (J 131 563 1946) straw hat sizing id (J 132 894 1946) playing card sizing, Peterkin (ADS 58 249 1948) textile dermatitis, Gaul and Underwood (JID 13 1 1949) phenol Formol resin in a medicine Jordon (ADS 62 671 1950) shoe linings containing resins, Hitschmann (ADS 61, 679 1950) vinyl plastic tablecloth Pirila (ActaAllergol 6 82, 1953) resin cellulose worker sensitivity to phenol-formaldehyde resins Smith (AD 1 212, 1955) epoxy resins and amine hardeners, used particularly in aircraft industry.

War Materials.—The occupational hazards in war industries include those of cutting oils rust preventatives (chromates) electroplating welding and soldering defatting agents cleansing agents, explosives and poison gases (Schwartz IndustM 11 457 1942 Downing NEngJM 227 539 1942)

While TNT can cause acute yellow atrophy its principal hazard is a dermatitis which resembles pompholyx. It induces sago-grain vesiculation of the hands and erythema of flexures and sites of friction with clothing (Eddy and Tomb TriStateMJ 14 2751 1942) to which hardening often takes place.

Tetryl (trinitrophenylmethylnitramine) is an explosive in the manufacture of which workers routinely develop dermatitis with itching burning erythema edema epistaxis, sneezing and coughing and a typical yellow staining of the skin and redness of the hair. Most workers undergo hardening and may persist with their work (Schwartz J 125 186 1944) Fulminate causes discrete erythema of hands, forearms and face (Swanson BJD 56 44 1944)

Ammonium nitrate irritates wounds even leading to ulceration and slows healing. Smokeless powder may cause mild conjunctivitis and has been known to provoke urticaria. A clean shop protective clothing and adequate rinsing are useful control measures. Schwartz's protective cream, containing ferrous oxide 1 to 2% in a water miscible base, is helpful to tetryl workers (Witkowski et al J 119 1406 1942) A special soap incorporating 10% potassium sulfite takes off TNT and tetryl, with which it reacts to make a brown stain (Norwood IndustM 12 206 1943)

War chemicals are designed for various purposes and include signaling and obscuring smokes incendiary agents such as magnesium thermite and phosphorus and agents primarily injurious to enemy personnel, such as lachrymators, sternutators, vesicants, pulmonary irritants and systemic toxic substances (Cole et al ADS 39 45 1939) See Norris (J 71 1822 1918 Goldman and Cullen J 114 2200 1940 Sulzberger et al JID 8 365 1947 Prentiss Chemicals in War McGraw Hill 1937)

Mustard gas $(CH_2CH_2Cl)_2S$ is a vesicant, a primary irritant and a sensitizer. The effects are delayed 2 or 3 hours in onset, then there appear

nausea and vomiting burning of the eyes pain in the throat, and hoarse cough, intense conjunctivitis temporarily blinding the victim redness of the skin followed by blistering and brownish staining of the exposed skin and the flexures, and inflammation and necrosis of pulmonic mucosae leading to septic bronchitis and bronchopneumonia. Death results ordinarily only as a result of septic complications and later than the first day Intense exposure may produce gangrene Moist skin is more susceptible than dry skin (Renshaw JID 9 75 1947) Prompt washing with green soap greatly reduces the severity of the lesions. If the chemical is allowed to remain on the skin the burns are deep and severe although comparatively painless at first One may immerse the injured parts in Dakin s solution, the strength being about 0.5 per cent hypochlorous acid or weaker or use applications of wet dressings saturated with the same solution Dichloramine T in chlorozone or chloramine-T in sodium stearate may be used. Greasy dressings are not good. With extensive bulla formation protein loss is consequential and the case is fundamentally like an extensive burn to be managed with regard for plasma replacement shock and secondary infection

Lewisite an arsenical mustardlike poison of great potency produces erythema and bulla formation along with arsenical intoxication. British Anti Lewisite (BAL) is 2,3 dimercaptopropanol which given intramuscularly in an oil solution is an effective antidote

See Lymphoblastomas, nitrogen musta d t eatment; also Davis (J 126 209 1944) Cullumbine and Liddell (JID 68 291, 294, 1946) penetration of a tissue ointment containing chlorine Alexander (Milsurg 101 1 1947), casualties from accidental explosion Sinclair (BMJ 2 290 1948 1 476 1949 1 346, 1950; JID 61 113, 1949) clinical features, treatment, experimental exposure, Cox n (J 122 438, 1943), lewisite eye injuries instantly painful, different from mustard, Sulzberger et al. (ADS 56 10, 1947) BAL vehicle and protective efficacy Keumand (be YBD 1950 p. 391) experimental nitrogen mustard sensitization.

Tear gas (CN) may cause vesicular dermatitis and is a sensitizer (Ingram BJD 54 319 1942) Tear gas burns are treated with weak alkali washes.

Diphenylchlorarsine (DA) is detoxified by chlorine water or KMnO

Radiation injuries of all degrees of severity and of local or general extent may result from atomic fission (see Atomic Energy Injuries)

Prognosis of Dermatitis Venenata.—Elimination of the cause is usually followed by recovery within a few days or weeks. Clinical *restitutio ad integrum* is only apparent hypersensitivity generally remains. Repeated attacks or continued persistence of disease is expected until the cause is successfully escaped from although it is certainly not necessary always to identify the cause in order to escape from it (Sutton ADS 59 30 1949) A known and carefully avoided irritant may be met accidentally or inadvertently

The effort to hyposensitize is not likely to be practicable or helpful. It is seldom the line of attack. But sensitization may disappear if contact is avoided for many months, or the degree of sensitivity may diminish greatly Despite persistent contact with an irritant some persons become hardened to some allergens. This fact surely accounts for a proportion of the practitioner s tedious cures of difficult cases

Allergic react v t sometimes disappears spontaneously When the skin w re tested afte a int rval of 1 t 3 ears duri g whi h an irritant had been avo ded and the ki had remained healthy reactivity t th original rritant wa found to have been lost in some 67% of the patient reported Gomez Orbaneja and Barrientos (abs BMJ 59 1939) Repeating patch test patient known to have been reacti e 20 years previously, Nielsen and Bang (Act D V 34 110 1954) fou d that allergy had been lost by 90% f those previous rritated by perborate washing powde , but by only 18% of those previous reactive t iek L About 25% of those wh voided substances to which they reacted positively neverth less had ee mateu relapses No patient showed an increase of hypersensitivity

Prognosis is materially influenced by treatment for patients and even doctors commonly a l l t the injury by their therapeutic efforts. The insistent urge to put something n a rash is an impulse hard to resist (Gaul J 127: 439 1945)

The outcome in dermatitis venenata is influenced by the nature of the irritant and the social economic and intellectual status of the patient. The aged farmer attached to his land and unable to learn a new way of earning a living and unwilling as well as too poor to move is going to continue to have his ragweed dermatitis, for he and his allergen cannot be separated. Many a patient is so lacking in resourcefulness that he is repeatedly *damaged by the same* irritant even when he knows what it is. A *patient's stupidity if it* exists is a great handicap to himself and to his medical adviser for there is no way to force a repetitiously injured skin to heal.

Complications.—The principal complications of contact dermatitis are (1) secondary medicinal chemical irritation (2) secondary extrinsic bacterial fungous or mixed parasitism (3) dermatitis medicamentosa from antigens given with the hope of hyposensitizing and such drugs as penicillin to combat secondary infection (4) focal infections, which maintain a supply of pathogens residing within the body and so impossible to eliminate by means of topical medication (5) imperfections of nutritional and endocrine balance such that the patient fails to heal himself as a normal person would and (6) combinations of these. All of these complications are commonly not rarely at work. When a dermatologist knows contact dermatitis and its complications, and is adept at unraveling them and dealing with them effectively he has become a master of his work. See Dermatitis of the hands.

The wise choice of external and internal medication is requisite remaining alert to intolerance. Patch tests with proposed medicines may be worth doing (Goodman and Sulzberger ADS 35 944 1937) although I and my patients seldom have the leisure for this and discover our mistakes, when they occur the hard way.

Relative to secondary parasitism, it is to be recognized that once the corneum is disrupted and especially when it is anointed with greases, bacteria which would be transient on normal skin are able to produce disease. This explains the commonplace development of vesicular and spreading staphylococcic dermatitis under the housewife's rings, where detergent accumulated in an unrinsed film, damaged her skin and abetted parasitic invasion. Contact dermatitis of the feet is likely to become infected with fungi already present but of previously trivial pathogenicity. Contact dermatitis of the face and neck is often complicated by the spread of seborrheic dermatitis from the scalp. Contact dermatitis often exacerbates lichen chronicus simplex (q v).

The effect of focal infection is obvious in many cases of occupational or housewives dermatitis of the hands. The worker's skin is irritated by cutting oil or cleansing agent and does not heal when contactants are eliminated. Until the infection of pyorrheic gums or abscessed teeth is eradicated, or the erosion of the cervix uteri is cauterized, dermatitis persists.

Chronic dermatitis in which contactants are an initiating factor are frequently not responsive to therapeutic effort until the overingestion of caffeine is corrected or the underingestion of protein or the inadequacy of the body's own production of thyroxine or estrogenic hormone or until iron, vitamin B (especially B) and liver extract or cortisone or ACTH are given in adequate and effective doses. see Sutton and Ayres (ADS 68 260 1953).

A complication rarer than it used to be yet requiring a word of warning is injury from unwise x ray therapy. For contact dermatitis may under x ray treatment temporarily recede to the delight of the patient only to relapse and receive more treatment repeatedly until disaster has come about.

Chronic dermatitis presumably initially contactant may undergo lichenification and manifest the features of Lichen chronicus simplex (q v) including autoeczematization phenomena. The best explanation seems to lie in the nature of the soil the patient's peculiarities with especial reference to imperfections of nutritional and hormonal balance. Lichenification may occur as one form of response to chronic irritation.

Treatment of Dermatitis Venenata.—The basic principle is to eliminate contact with the irritant. One must give the patient symptomatic relief while the skin heals. *Primary effort is directed at keeping something off the skin, not at putting something on it.* No medicine can force an injured tissue to heal. There need be no haste to identify the cause. Remove all likely causes, relieve the patient, then seek the cause. In selecting palliative medicines, remember that "what you don't put on don't give no trouble" (Davies, BJD 65 388 1953)

If contact has occurred within a few hours but reaction has not as yet set in, then the removal of the irritant from the skin may be possible. Soap and water or alcohol at this time may be urgently needed and successful, whereas, a few hours later this same treatment would do harm. In ivy poisoning allergen may be present even after reaction has set in.

Chemical neutralization of many dermal irritants can be accomplished. Sodium thiosulfate is the antidote for iodine and chromates, sodium bicarbonate for formaldehyde and potassium sulfite soap for TNT for example (Anderson ADS 49 176 1944)

Prevention of contact may be achieved by discarding objects, such as shoes or furs. Often it is difficult to convince a patient that one solitary momentary contact is sufficient to undo the benefits of two weeks of isolation. Sometimes mechanical means (gloves, petrolatum, boots) or chemical means (baths, soaks, detoxifying agents) may be used to interrupt the contact or the sufferer may learn what not to touch, or where not to spread the contact or a workman may be shifted to a different job so that his contacts are different. Chemicals nonirritant to a given worker may be substituted for irritants. Protective ointments are a last choice not a first one in industrial dermatitis, though they encourage the worker to wash. Better measures are a clean tidy shop with equipment designed and processes planned to prevent contact with hazardous chemicals, and ample facilities for use of clean clothing and selected cleansing agents so as to minimize the workman's contacts (Schwartz)

Such solutions are easy comparatively if the allergen is known. But some allergens are so widely disseminated or of such ubiquitous occurrence that avoidance may be difficult. Nitrocellulose wax and sulfonamides are such agents. One may apply talc to keep the skin dry rather than grease which would simply cause particulate irritants to adhere the more. It may be impossible to move the individual from his occupation or to protect him or to desensitize him as in some cases of ragweed dermatitis.

When the allergen is not known, the avoidance of every likely agent is desirable. Unless the patient is considerably distressed by his disease he will not ordinarily be willing to be hospitalized, but hospitalization, with complete control of the environment, separating the patient from his home clothing hair tonic toothpaste, garden, potted plants, sofa cushions and insect powder is an effective way to bring irritation under control.

When the Injurious Agent Is Unknown but the diagnosis of chemical injury by contact is presumed, the technic of cure may be put in algebraic form (Sutton JIlo SMA 44 431 194) Let chemical items a, b, c be all the chemicals capable of injuring the skin; then

$$a \quad b + c \quad = \text{disease}$$

Let no item touch the skin unless it is extremely likely to be harmless. Then

$$a \quad b + c \qquad a - b - c \qquad = 0$$

If all contacts except trustworthy ones are in fact removed, disease will disappear within one or two weeks; rarely is a longer time required. If disease does not steadily fade but does flare after the effort has begun, the implication must be accepted that, while the theory is right, the practice has failed, so that effort must be redoubled to make certain that an unidentified injurious agent or an irritating medicine will be eliminated.

After elimination has succeeded, as attested by the fact of uninterrupted improvement, then, of a, b, c at least one item is injurious. The status of the patient at this moment perhaps one or two weeks after the initial instruction in the avoidance of "everything," is a relieved but disaccommodated status of freedom from disease and isolation from all contacts. The task is half finished, and the patient's skin is now ready

to serve as the testing ground for the item previously eliminated. If contact with all were replaced at once no information would be gained from the subsequent flare. But if a is replaced, and 24 hours later b is applied, and later c according to a written tabulation of items to be tested by schedule, then identification of the poisonous item is straightforward. For on contact with that item the disease flares, usually first evidenced by itching which starts within 4 to 8 hours. If a, b, c are so replaced in their usual form of contact at 24 hour intervals, then classification of a and b and c into sheep and wolves is a matter requiring rarely more than one week of purposeful effort. It is common to relieve the patient in one week and to identify the cause in another two weeks of endeavor accomplishing complete cure in a month or less.

When the patient is first seen, the fact is that patient and doctor cannot know what chemical caused the disease. One does know however that the causative chemical must touch the skin, be it constantly or infrequently. One therefore orders the patient to let nothing touch the skin except those chemicals which are most trustworthy and least open to suspicion. These are the safest and most trustworthy chemicals:

(1) air if it is not contaminated with soap particles, perfume or such
(2) water
(3) petrolatum (not invariably "safe")
(4) cellulose, such as cleansing tissues, cotton or linen uncontaminated with detergent, dye, laundry starch or fabric finish
(5) hands (*which are going to touch an itchy skin, one may be sure*) if they are not contaminated with nail lacquer, cold cream, soap or the like
(6) selected textiles: a textile including garments for day and night wear may be judged "safe" if it was touched repeatedly without harmful effect during a six-month period prior to the onset of dermatitis. Request the patient to sort his garments by this criterion, item by item, into two groups. He wears and touches the "safe" ones only and sets aside the doubtful ones until the time comes for testing items later. A seemingly "safe" garment may be contaminated by cleaning fluid, insect repellent, cologne, etc.

Technic of Elimination of Irritants According to Location of Disease
(Sutton, AD&S 59: 36, 1949)

Instructions vary in cases affecting various parts of the body. If contact dermatitis is limited to the scalp, for example, it would be silly to advise the patient to wear predermatitis shoes. One has also to take into account the ecologic situation. The patient must eat, sleep, be clothed and do certain unavoidable tasks. A wealthy unemployed single woman presents a different problem from the housewife who is economically incapable of hiring help and is responsible for several small children and an ailing mother. One must give instructions which can be carried out. The patient is asked for a maximum of two weeks of intensive effort at eliminating contactants, for this is long enough to do the work and short enough to get cooperation. The patient is caused to understand that elimination means 100 per cent and that 99 per cent is not good enough. Even obtuse patients, if not hopelessly stupid, can be induced to comprehend.

Dermatitis Limited to the Scalp.—Omit medication, shampoo, lacquer, hair tonic, brush, hat, hair pins, perfume, *barber shop or beauty parlor*. See that hands do not convey an irritant, such as nail lacquer. Cleanse scalp and hair by prolonged spraying or showering with tap water (the "fire hose treatment").

Dermatitis Limited to the Face.—Omit medication, every toilet article and cosmetic, soap, dentifrice, mouthwash and eyewash. See that hands do not convey an irritant to the face. Cleanse with water and petrolatum. Brush teeth with baking soda. Shave with electric shaver. Wash dishes with a selected cleanser so as not to contaminate the hands. Eliminate textile, scalp and neck contactants.

Dermatitis Limited to the Neck.—Omit medication, every toilet article and cosmetic, soap, perfume, and jewelry which may touch the neck. Eliminate textile and face contactants. See that hands do not convey an irritant to the neck. Cleanse with water and liquid petrolatum.

Dermatitis Limited to the Region of the Trunk.—Omit medication, every toilet article, soap and cosmetic which touches the trunk. Control textile and neck contactants and those conveyed by hands. Check metal fasteners, menstrual accouterments, contraceptives, mat hes, dress shields, bust pads, cleansing or antiseptic agents applied to the bathtub, rubber pad and hot water bottles, insecticides and cleaning fluid or laundry starch (which contains borax) in textiles which might explain exceptions if safety of the

garment were judged solely by its age. Cleanse with water. Prohibit use of water softening agents. Use corn starch for powder and baking soda for underarm deodorant. Use petrolatum on babies, not olive oil or antiseptic oils.

DERMATITIS LIMITED TO FEET AND LEGS.—Omit medication, soap, depilatory and leg makeup. Control textile contactants and those conveyed by hands. Judge shoes and slippers by the same criteria as textiles. Check for weeds, irritant dusts, floor waxes, paints and cleansers. Women rarely possess safe old stockings; they may risk the purchase of silk or cotton hose, wear bobby sox or go bare-legged. Soap splashed from the washing machine may irritate legs. Nail lacquer is sometimes applied to runs in stockings. Presumably safe, old shoes may be contaminated with medication. One may buy a pair of new shoes and wear them exclusively; either they are harmless and the foot disease fades, or they are not and the feet get steadily worse so that security of the foot gear may be judged positively. Launder hose with mild toilet soap.

DERMATITIS LIMITED TO DISTAL UPPER EXTREMITY.—Omit medication and all cosmetic and toilet articles which may touch the hands. Control face and scalp contactants, for these are applied with the hands and hair tonic, cold cream or dentifrice may irritate hands without irritating the head. Cleanse hands and body (hands must hold the soap to wash other parts) only with water and petrolatum. Wash dishes with hot water only or delegate the job without drying dishes which have been washed by others. The patient should wash her babies only with water for the two-week period. Avoid baby oil. Stop baking (see Food handlers). Omit every household cleansing and polishing agent and gloves, including rubber gloves. Judge purses by criteria of safe textiles. The usual irritant of hand are bleaching agent and toilet and cosmetic articles. However paints, paint remover, plants, sprays, materials for all sorts of needlework, chrome nickel and lacquered fasteners, glue, cement, gewgaws and gadgets, chemicals met in hobby, business or recreation—all are open to suspicion. Employees may have to be taken off the job in order to eliminate the unknown contactant.

Cases of dermatitis of the hand (q.v.) are harder to solve than others, but the reason for this proves usually to be that the dermatitis is not purely contactant. Few cases of dermatitis of the hand of two or more months duration are of uncomplicated contact dermatitis. Occlusive dressings may be used, of course, and, if improvement is not obtained in a week, complicating factors may be assumed to exist.

DERMATITIS AFFECTING THE SKIN IN MORE THAN ONE OF THE LISTED LIMITED REGIONS.—Since any distribution is a sum of some combination of the limited distributions already considered separately, add together the elimination efforts for each region involved.

ILLUSTRATIVE HYPOTHETICAL CASE PRESENTATION.—June 1. Mrs. X, 30-year old white woman, requests medical service because of itchy eyelids. The skin of the lid is wrinkled, leathery, flaky, excoriated, but not exudative. Disease has existed with no great change in intensity and no conspicuous flares for 3 years. There is no other disease or area of dermatitis. The interview:

Madam, your skin disease is caused by some chemical which touches your eyelids. Germs are not concerned, and your interior food or function, is not pertinent. No medicine exists which will make your eyelids heal. You will be cured, and you can be cured only by avoiding that which on touching your skin poisons it. You and I, as we sit here at this moment, do not know what poisons you.

Then, doctor, how can I escape the poison?

If nothing touches your face except chemicals which are harmless, then surely your disease must fade and disappear. In order to eliminate all contacts except the probably harmless ones, you will be put to the trouble of eliminating many chemicals you didn't need to—we shall eventually know which chemicals are which—but for the next week, I want nothing to touch your face except (1) air (you can't avoid it, but you don't need to contaminate it by scattering soap powders indiscriminately); (2) water (it is harmless—things in water are often harmful, but water is not); (3) petrolatum (I have seen only people in 25 years of dermatologic practice whose skin would not tolerate petrolatum); (4) old cotton or linen garments, towels, sheets, and pillowslips (do not allow residual soap, starch, bluing or bleach to remain in these please; but the cell loose of which they are composed is trustworthy); (5) hands (which must be free from lotions, creams, nail lacquer, etc.); and finally (6) the utensils and foods you use in eating (silver and china are harmless, and you've got to eat).

My face may be touched by nothing but air, water, petrolatum, cotton or linen, and uncontaminated hands? I may eat and drink what I wish? All right, doctor, but how do I wash, or clean my teeth or relieve my itching?

I have listed the things you may touch, a short positive list. I have not tried to list the multitudinous things you may not touch for the negative list is not short and is not determinate. If I don't say touch it, don't. Wash with water and dry with a towel. You won't be as clean as you like, but you'll be as clean as you need to be. Cleanse your teeth with table salt or baking soda—I can trust them—after all, you'll only have to live this way for a week or so. Wash your hair with Prell (I have seldom caught it doing harm) and do this right away, because cosmetic articles on hair especially lacquer often cause dermatitis. Use Marcelle lipstick and powder if you must,

for they are designed to be hypoallergenic; you may use the lipstick for rouge and do not need to buy a lot of things. Do not throw away your old cosmetics, which are expensive, for we do not know a yet what you will have to discard or avoid—we shall find that out later Instead of a y kind of cold cream use mineral oil (not baby oil or olive oil) and petrolatum. These are not so ba l a lubricants, you will fin l

As for relief of itching use just enough petrolatum to keep the skin from feeling as if it would crack, and lay on your itchy lids a towel wrung out in cold water Petrolatum would *not* be suitable if your trouble were poison ivy; it would spread the irritant around. Apply the cold compresses for as long as you desire any time you desire. They will relieve you a well a any medication we could choose and cannot harm you. Among the many things you may *not* touch are soaps of any kind, rouge creams, perfumes, shampoo medicines hand lotion, and nail lacquer I think it was Balzac who said A woman smells best when she doesn t smell at all. Do not put any medicine in your ears, eyes, nose or mouth or on your skin unless I know what it is and approve of it

What makes me get well, doctor if I do nothing but avoid a poison?

An injured ski i analogou to an injured bone In treating a broken bone, the physician basically puts its ends together and leaves it alone It heals itself *Th ski will heal when nothi g interferes with its heali g* In the case of the fracture the patient requires morphine perhaps or aspirin, but medicines do not cure him. They enable him to live more or less comfortably through the period of time that healing requires. The cold compresses and petrolatum will do for you what the sedatives do for the patient with the broken bone

June 8 Mrs X returns, stating that her eyelid did not change much for the first 3 days, then improved steadily There wa no flare itching became less and the cold compresses a d petrolatum proved comforting Impro ement is visible

We may j dge the doctor say that you have successfully avoided the poison, although this has inconvenienced you to some extent. We must now arrange for you to live normally instead of livi g in chemical isolation. Of the many things you have been de ied what would you like to put on your face first?

Soap then my rouge powder a d cold cream. If I could use these I d be satisfied.

We must plan these contacts so that if any one of them flares your disease we will recognize it. Write down a list of items to test and test one each day designating of course the particula brand of t let article you propose to try Apply one item each day in the manner i which you ordinarily apply it Let me see you when your disease flares. Do you understand you instructions?

Perfectly doctor This seems almost too easy Other physicians gave me x ray treatments, intravenous and other shot , a cabi etful of expensive prescriptions the alphabet of vitamins and quite a series of food allergy tests. Why for two years, before I met you I ate no eggplant o kohlrabi whatever and nevertheless itched furiously

The therapeutic technic of othe physician is not a proper subject for comment but it may be said that not all human beings are guided exclusively by crystalline in tellectual function. I myself have prescribed a blood purifier; I was weary at the time and the patient asked for it Follow your instructions, and let me hear from you.

June 1.. Mrs X returns, he lids swollen, red and itchy She says, Doctor I used my favorite soap the day of ou last i terview rouge the ext day a d powd the e t without trouble But last n ght I ppl ed cold cream a I retired. This morning my lids were again swollen and itchy

You and I now know that thi bra d of cold cream poisons you the physicia explains. You will get ove this flare in a few days. Use the cold water compresses as you did before. When you have cleared up try Bla k s brand of cold cream. The Journal accepts this firm advertizing which claims that few people are allergic to its p oducts. Seldom indeed do I find a person being poisoned by more than one chemical, although it i not rare for an indi idual to meet his poison i several different guises. T ke for example Mrs Z whose poison wa n trocellulose. A few years ago, he spectacle frames, th handles of her bru h a d comb and her patent leathe slippers and handbag each poisoned her She and I finally worked that problem out, but she late flared after handling p g pong balls A f you, howev I surmise that your troubles are over

Doctor my appreciation knows no bounds.

You cure was accompl hed, madam by prescribing nothing fo you, with meticlous care

Difficulties occur when contacts believed to have been eliminated never theless are made A woman with itchy eyelids, who cooperated intelligently experienced a flare-up after playing cards the sizing of the washable cards was carried to the face by the fingers, previously imagined to be not con taminated A patient with dermatitis of the face from menthol experienced a flare up when she sucked certain cough drops. A man with dermatitis of the dorsum of the left hand was intolerant of the dentifrice with which he cleansed his dentures which he held in the left hand and rinsed with the right

before returning them to his mouth. One must be alert to chemicals put into ears, eyes, nose mouth rectum or vagina The expert is cognizant of all the things that persons of various ages and both sexes do and touch

Difficulties occur when the contactant is an occupational one for the patient if he is to be on the job at all must make contact with many possibly harmful chemicals. The disease in such patients can be proved occupational by (1) excluding all contactants except occupational, (2) observing that the disease continues and then (3) removing the patient from the job and finding that the disease disappears. *Prior to returning the patient to his job patch tests with chemicals met occupationally are necessary*

I do not say that patch testing may be wholly dispensed with but a great deal of patch testing may be neglected and the practice of dermatology may thereby be improved in efficiency

SKIN TESTS are discussed in the pages devoted to diagnosis. One use of them is to pass the time required for the patient to heal (Gaul: J 1*7: 439 1945) I do not emphatically decry the use of skin tests for investigational purposes. While patch tests would have to be used to determine the particular noxious ingredient of a face cream, another cream can be substituted successfully in all probability so that neither the patient nor the physician ever learns what chemical substance was in fact harmful, for it was neither necessary nor expedient to find out Indeed I am willing to cure a patient without ever knowing what was the matter with him, exactly

FAILURES occur when the disease is not pure contact dermatitis. Secondary infection must be recognized and dealt with by means of nonirritating antiseptics. Primary infections may simulate contact dermatitis. Foci of infection may profoundly influence what starts as contact disease In chronic dermatitis of hands or feet especially the elimination of contactants combined with the elimination of focal infection comprises an attack which is often curative Atopic dermatitis does not yield to elimination of contactants, although such elimination contributes to the patient s welfare

Allergic dermatitis may persist for days or even weeks after the cause has been removed. It is during such a refractory period that a physician, impatient for benefit in a case of distressing dermatitis of unknown external cause changes from one medicine to another in the futile expectation of finding something that will bring about healing In shifting from one application to another great risk is run of applying a medicine to which the patient is sensitive One does best by prescribing the simplest and blandest of agents and adhering to their use if one is sure that they do no harm The evils of overtreatment have been stressed by many authors, notably Gaul and Underwood (IndianaSMAJ 40 17 1935) Exfoliative dermatitis has resulted from the application of ammoniated mercury ointment to some minor inflammation with the development of spreading mercurial dermatitis not recognized as such and treated with more mercury

Explanations of why occupational cases may fail to clear include according to Morris (ArchIndustHyg 10 43 1954) failure to follow advice overtreatment, failure of hardening incorrect diagnosis, bacterial infection dermatitis medicamentosa tinea of the feet inadvertent contact with the irritant nervous upset physical trauma stupidity in following treatment advised, *preference of patient for compensation rather than cure* flares incited by patch testing atopic background, accentuation of pre-existing disease focus of infection avitaminosis Morris called attention to the cures achieved by the lump sum settlement, the monetary pay-off constituting a magic green salve

OTHER THERAPEUTIC MEASURES.—X ray therapy desensitizes locally This is, hypothetically due to destruction of fixed cellular elements responsible for sessile antibodies. Reactivity generally returns within from 1 to 3 weeks after this nonspecific desensitization. If the same dermatitis is treated time after time with x rays, the eventual result is an x ray burn. The dermatitis produced by dinitrochlorobenzene was not influenced by x ray therapy in the experiments of Kemp and Kligman (JID 23 423 1954)

Benadryl and other antihistamines are helpful when an urticarial element is prominent in the reaction of the patient to the poison, but in fairly pure epidermitis these do not allay (Blumenthal and Bostenberg MAnnDC 16 86 1947) Topically they are hazardous often irritating

ACTH and cortisone may be helpful in the palliation of severe cases especially if the dermal reaction is considerable (see Poison Ivy)

Sodium thiosulfate intravenously 0.5 Gm the first day and 1 0 Gm the second third fifth and seventh days, was said by Ormsby (MichSMSJ 37 135 1938) to aid in overcoming hypersensitivity I doubt its efficacy

The simplest of medicines are satisfactory In acute dermatitis of contact origin, the skin may be freed of previously applied greases by means of benzine White petroleum jelly is put on to protect denuded nerve endings, and soft clean towels, wet with plain cool water are superimposed This is comforting and it is bland The patient is denied coffee and may be given aspirin 5 grains every three hours unless intolerance occurs. What the tired itching patient wants is respite from bedevilment by his skin then he will sleep Compresses should be moist not dripping and cool and should act like a blotter in absorbing exudate rather than rendering the skin soggy and macerated They should be left in place not longer than half an hour but may be repeated as frequently as the patient desires. If they are medicated they should not be allowed to dry on the skin, for as the water evaporates the concentration of solute increases until it may irritate They should not be covered with an impervious wrapping Aluminum acetate half a level teaspoonful to a quart of water made up in a milk bottle and poured from that onto the towel is convenient and satisfactory

Barrier creams may be of water repellent or oil repellent types. Several commercial preparations of elegance and excellence are readily obtainable Such an innunction can serve as an invisible glove which is applied prior to exposure of the skin to the irritant and which washes off readily after exposure Of greasy agents for repelling water solutions petrolatum is the best Mason in 1946 showed me his technic for testing barrier effectiveness of ointments and proved that lanolin and petrolatum are both impenetrable in a layer 1/5000th inch thick while the particles in zinc paste render it more pervious than simple petrolatum. See Sadler and Marriott (BMJ 2 769 1946) Schwartz et al (Occupational Diseases, Lea & Febiger 1947 p 100) complete with formulas. A silicone preparation with nitrocellulose in it to prevents its washing off has evinced some value (Smith et al. JID 21 111 1953 Covicone) Silicone protective creams tried by Morris (ArchIndustHyg 9 104 1954) proved unsatisfactory

Treatment of Complications obviously presupposes the recognition of them When a patient gets worse instead of better the first thoughts are concerned with failure to escape from injurious agents and possible irritation by medicines. Bacterial secondary infection (see Infectious Eczematoid Dermatitis) should be fairly evident The usual invaders are hemolytic *Staph aureus* or hemolytic streptococci or both When *B proteus* or *Ps aeruginosa* enter in, difficulties may be considerable for these are sometimes hard to get rid of. While in my practice the mainstays of treatment of bacterial infection are potassium permanganate soaks, tetracycline ointment or Vioform Cream incorporating Chloromycetin 200 mg per ounce I also often use antibiotics by mouth seldom by injection. It is highly advantageous to have available reliable laboratory assistance for antibiotic sensitivity tests.

When topical and internal antibiotics fail, then especially is one suspicious of the presence of significant systemic derangement It is typical in a case of focal infection for injections of penicillin to help the patient only temporarily Common foci are pyorrhea, dead teeth cervical erosion and cystocele I am dependent on competent dental gynecologic and urologic consultants when I am responsible for the care of a difficult patient See Chronic Dermatitis of Undetermined Cause (p 879)

The errors of metabolism which most often interfere with a patient's ability to heal are excess of caffeine and inadequacy of protein. Many a patient slow to respond to medical effort is anemic and one likes to know the red cell count hemoglobin, color index and blood serum total protein. Daily in managing chronic dermatitis of which contactant irritation comprises an etiologic factor but not the whole explanation I endeavor to correct metabolic deficiencies using high protein diet iron and vitamin preparations, injections of liver concentrate or of vitamin B_{12} (presently I am of the notion that 600 micrograms of B_{12} intramuscularly helps almost anything!) and thyroid, estrogen or cortisone when indicated. Any individual deficient in thyroid or estrogen is better off for receiving a correct dose of it. Cortisone is often extremely helpful in palliating difficult stages of dermatitis of mixed etiology particularly when lichenification and autoeczematization are factors.

Seborrheic dermatitis (q v) can be attacked successfully by treating the scalp improving the patient's nutritional and hormonal balance and using topically a ½ or 1% coal tar ointment.

Secondary infection with fungi is due usually to a trichophyton from the feet or toenails, or to monilia. The combination of fungus infection secondary infection with bacteria and injury by chemicals is by no means a rare one. Potassium permanganate tetracycline 2% sulfur in Vioform Cream the control of contactants gentle débridement rest elevation drying in air attention to foci and perhaps cortisone are the usual therapy.

Fatigue exerts a deleterious influence and nothing is so exhausting as nervous tension and anxiety. Patients with extensive dermatitis need sedation, sympathy and psychotherapy. Hospitalization is not a last resort but should be used without hesitation for the benefits are likely to be economical, in the long run. A patient in hospital is not only segregated from unknown contactants but obtains respite from responsibility and pressure and generally does well.

POMPHOLYX

Symptoms.—Pompholyx is a variously caused syndrome manifested by vesiculation of the thick epidermis of hands and feet. Vesicles characteristically *appear in crops, are deeply seated and symmetrically located and* usually affect the fingers and palms. At a given time the vesicles are of more or less the same size. Representative of epidermitis (q v) and minute in their early development, they may progress in severity even to an extreme degree. The disease usually involutes without exudation after a few days, and exfoliation follows, often taking the form of tiny expanding circular scaling lesions. Itching is intense during the active stage. Secondary infection may occur especially when salves are used in treatment. Recurrent attacks are typical.

Whatever the chemical may be that causes vesiculation of the thickest epidermis and the clinical syndrome of pompholyx its prolonged and extreme effect, when this occurs, is to damage thin epidermis also so that there develop macular and edematous erythema and eczematous dermatitis which spreads symmetrically on the arms, the sides of the neck and face and the eyelids. The clinician would then give the disease a different name.

Etiology.—Pompholyx is a cutaneous reaction representing epithelial damage. Many cases are straightforward dermatitis venenata while others are dermatophytids, responsive to suitable treatment. Dermatophytosis of the feet, *onychomycosis* and *vaginal moniliasis* are causes easy to discover. Muende (BJD 46 479 1934) estimated that half the cases are secondary to dermatophytosis elsewhere. The lesions of pompholyx are free from ordinary parasites unless secondarily infected. They seem to depend for their existence on deleterious chemicals either directly contacted or absorbed from the metabolism of parasites located at a distance.

B endoperasiticus was identified in cultures from unbroken vesicles and named by Benedek, who undertook to prove its etiologic relation to pompholyx (UCutRev 60: 467 1946) and prepared from it a vaccine which he believed therapeutically valuable a view confirmed by Schuster (NoWM 46 298 1947). See Sutton and Ayres (ADS 69: 208, 1953)





Fig 131 —Pompholyx. Note fine vesiculation of dorsa and sides of distal digital skin.
Fig 132—Pompholyx secondary to vesicular dermatomycosis of feet

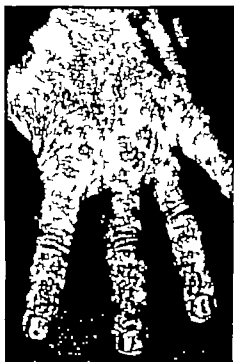




Fig. 133 —Pompholyx. Compare epidermophytid of Peck (ADS 22 40 1930)
Fig 134 —Pompholyx, histopathology intra-epithelial vesiculation of palmar skin.

Trichophytin or ragweed injections in overdosage may provoke attacks in sensitive persons. Hyperhidrotic individuals with psychosomatic difficulties are especially subject to pompholyx, of which not all cases are fully understood. In ʺ selected psychoneurotic patients (Goldman: MBullUCincinnati 8: 79 1941) mecholyl injections provoked exacerbations, while various other agents that act on the vegetative nervous system did not influence the disease.

Histologically the vesicular lesions are not related to the sweat ducts or pores saving by coincidence. Sutton (J 61: 40 1913) showed, confirmed by Shelley (ADS 65: 314 1953) among others, neither pilocarpin nor atropine influenced the quantity of vesicle fluid, which did not contain iodine after iodide was given by mouth. The sweat ducts in f et long withstand the processes which affect adjacent prickle cells (Devine: BJD 64: 393, 1952). Sweat retention is not the explanation (Robinson: ArchDerm 3: 59 1877; Wilson and Thackray: BJD 64 402, 1952. Ascher: BJD 67: 9 1955)



Fig. 136.—Pompholyx, showing superficial intraepithelial vesiculation. (Miller ADS 56 678, 1947.)

Pompholyx-like eruptions may be classified (Callaway and Barefoot NCarolMJ 1 547 1940) as (1) mycotic, (2) allergic from contact fungi, or bacteria, (3) idiopathic, (4) toxic from food or drug, (5) chronic infectious dermatitis, and (6) associated with general skin diseases. Becker (NebrSMJ 26 419 1941) attributed many cases to functional perversion of the sense of fatigue. Davidson and Birt (CanadMAJ 49 97 1943) limited Hutchinson's name cheiropompholyx to those cases which are not contactant or dermatophytid, and stressed the fact that the rash is more common in hot weather. I think the disease is sometimes atopic (see p. 884).

Diagnosis.—The deep-seated vesicular character of the lesions, their symmetric distribution and their occurrence in crops are distinctive. Demonstrable parasites are absent.

Treatment.—Rest, elimination of contactants, and symptomatic relief are essential. Mild, soothing astringents, such as cold compresses of 1:500 aqueous aluminum acetate or 1:5000 potassium permanganate may be prescribed. Some patients obtain temporary relief by running extremely hot water over their hands. The lesions may be incised and drained. Suitable treatment must be directed against focal infection, mycotic or bacterial. Roentgen therapy is effective in fractional doses but must be prescribed with caution against overdosage. Drugs which inhibit hyperhidrosis, such as Banthine and Prantal, have considerable value in some cases. Cortisone 25 mg. b.i.d. by mouth, is likely to be effectively palliative.

DRUG ERUPTIONS

Dermatitis Medicamentosa is applicable to any eruption due to absorption of medicinal chemicals, differentiating contact dermatitis caused by medicinal agents (q v) One must distinguish intoxication from intolerance The latter comprises symptoms not normally produced by mere overdosage Drug eruptions may simulate almost any dermatosis, and careful investigation is likely to be necessary to identify puzzling cases. The lesions are likely to be *widely and symmetrically distributed and sudden* in onset and recurrence Drug eruptions result from administration of chemicals by ingestion injection, inhalation or inunction, or from absorption of them from their application to nasal vaginal anal, vesical or conjunctival mucosae or wounds, or through the pulmonary system milk, or placenta Sulzberger (Dermatologic Allergy) noted Clinical manifestations include eruptions which are erythematous, morbilliform scarlatiniform eczematous, exfoliative urticarial, purpuric gangrenous, keratotic vegetative acneiform furunculoid, dyshidrotic hyperpigmentary or depigmentary nodular or sclerodermatous, or which simulate erythema multiforme pityriasis rosea lichen planus herpes zoster erysipelas, or lupus erythematosus. They may even include alopecia or pruritus without a rush Aplastic anemia and death are sometimes caused by medicines.

Etiology.—The disease is usually accredited to idiosyncrasy which may persist indefinitely See classification of allergic phenomena drug allergy Abramowitz (NYSJM 37 128 1937) observed that passive transfer is sometimes possible Arsenical dermatitis may commence as Stokes and Kulchar (BJD 46 134 1934) noted at a dermatophytic focus.

The disease is not common. It occurred in about 1 of 2,000 patients seen at the University of Kansas Hospital (JKansMS 38 365 1937) The large majority and by far the most serious cases, were those due to the arsenical antisyphilitic remedies, and the fatalities which occurred were among these

Eruptions may be produced by minute amounts of a drug though in most persons the drug provokes no rash even in *large* doses. Drug eruptions recur when the same or perhaps when a chemically related substance is given. Identical eruptions may be provoked by dissimilar drugs. One drug may induce different manifestations in different persons. Specificity of drug sensitivity may be demonstrable Some drugs experimentally sensitize human and other animal skins. Drugs act like allergens in inducing diseases which exhibit incubation periods and subsequently altered reactivity to reexposure and variations in host susceptibility are notable Tuberculoid structure is rarely if ever produced however *Reagins usually* cannot be demonstrated Eczematous eruption may appear following internal administration of a drug after contact dermatitis has been produced by it Drugs may produce photosensitization, vasomotor disturbances nervous and visceral manifestations.

Mechanism product e f drug reactions were carefully considered by Hostenberg and Webster (J 154 221 1954) who listed (1) pharmacologic reactions to overdosage, exemplified by erythema *from* nicoti e acid or argyria from silver salts; ( ) enzymatic terference as acrodynia from mercury or light sensitivity from sulfonamide (3) idiosyncrasy as fungating lesions from iodide; (4) allergy exemplified by acute urti ria from penicillin chronic polyarteritis from sulfonamide or eczema from arsphenam e (5) Shwartzman phenomenon i ba Ht rate purpura (6) Herxheim phenomenon (7) ecologi effects a when monil asis follows Aureomycin and (8) biotropic ffects, f erythema nodosum from sulfathiazole These authors co sidered allergy o ly one mech nism of se ral ca sing d rmatitis medicamentosa, which by th ir semantics mean any derm tosis ca sed by pharmaceutical i ternally admi istered.

Arterial embolism when an oil emulsion i injected erroneously prod ces a typical syndrome of marmoraceous lividity soo *followed* by gangrene (Sulzberger nd Baer AmJS 4 60 1940) Intravenous inject on of such a medicine as bismuth subsalicylate in oil result in pulmo ary embolism and death. *Embolism followi g the se of sclerosing* agents n treatment of varicose veins is rare (Shelley J 112 1792, 1939)

Diagnosis is established if the eruption disappears when the drug is discontinued and reappears if a small dose is given experimentally Recognition

is facilitated by suspicion history and knowledge of the various potentialities of drugs for producing disease

Treatment.—Recognition of the cause and its elimination are essential. When one of several drugs might be the agent stop all of them The wider the assortment of drugs a patient receives, the less the likelihood of catastrophe resulting from their withdrawal. If gastric lavage or catharsis will remove unabsorbed chemicals, it is indicated BAL has utility in the metal poisonings, especially the arsenical ones. Silver pigmentation arsenical keratoses, and severe arsenical dermatitis became less common as wisdom in the use of medicines became more widespread and as the usefulness of these now old fashioned remedies diminished when better ones were devised.

Individual idiosyncrasies are to a considerable extent individually treated. The antihistaminics are palliative in urticarial cases. ACTH and cortisone are frequently of great value Calcium intravenously helps the painful erythema nodosum sometimes caused by penicillin but it rarely helps any other drug eruption. From the standpoint of the patient there is not much difference between drug allergy and poisoning

Overenthusiastic treatment of comparatively innocuous infections, so that dermatitis results, has no justification. Permanent relief lies in complete avoidance of the provocative agent

See Sulzberger and Wise (ADS 8: 441, 1933) eczematous drug rashes, allergen reaching skin from without or within; Wise and Sulzberger (PaMJ 37 973, 1934), dermatophytid and drug eruptions; Cipollaro (N YMonth 63 477 1936) dermatitis from drugs Sherman (J 140 447 1949) generalities; Stokes et al. (AmJMSci 218 440, 1949) survey and bibliography; Goldman (ConnSMJ 13 4 0, 1949) antibiotics Hermann (AmJMSci 218 446, 1949), recent literature; Carr (NEngJM 245 892, 935, 1951) review Flaxman (J 147 377, 1951) drug fatalities, 107 found in period 1947 1950, not all allergic; Percival (BMJ 1 809 1951), refresher review Peterkin (EdinMJ 58 41 1951), common examples Berkowitz et al (AnnAllergy 11: 561 1953) in pediatrics; Alexander (Reactions With Drug Therapy Saunders, 1955); Brown (J 157 814 1955) problems of drug allergy

TABULATION OF ILL EFFECTS OF VARIOUS MEDICINES

Acetanilide.—Generalized erythema. Methemoglobinemia.

Acetarsone.—See Arsphenamines.

ACTH.—Cushing's syndrome; hyperpigmentation acneiform eruptions, hirsutism, moon face striae atrophicae (Behrman and Goodman: J 144: 18 1950) Androgenic effects, including acne, seborrhea and seborrheic dermatitis (Brunner et al.: JID 16: 201 1951) Sodium retention. Urticaria (Feinberg et al.: J 147: 40 1951) ACTH acne lesions are small papules and pustules, erythematous and sore, monomorphous on skin that is not greasy disappear without scarring on withdrawal of drug (Sullivan: Trans ADA 1955) Anaphylactic death case (Hill and Swinburn Lancet 1: 1 1 1954)

Acetazolamide (Diamox).—Agranulocytosis (Pearson et al.: J 157: 339 1955)

Adrenalin.—Urticaria, possibly from chlorbutanol (Rubin: J 138: 626, 1948)

Alfalfa Seed Infusion.—Itching of forearms and face (Kaufman: J 155: 1059 1954)

Alpha Methopterin.—Exfoliative dermatitis, oral hemorrhages and ulcers (Meyer et al.: CaRes 9: 606, 1949)

Amidopyrine.—Neutropenia, urticaria, fixed eruption, bullae, agranulocytosis. See Unger (JAllergy 8 76, 1931); Bott et al. (AIntM 64: 26 1939) Ritchie and Spille (ADS 59: 437 1949); Discombe (BMJ 1 1270 1953)

Aminopterin.—Oral hemorrhage and ulceration alopecia leukopenia, folic acid antagonism, countered by administration of citrovorum factor (Schoenbach et al.: J 144 1558 1950)

Amphetamine (Benzedrine).—Rash resembling atopic dermatitis (Kanvar et al.: J 122: 1078, 1943) denied by Epstein (J 123: 54 1943) Causes coldness, blanching of extremities, erythema of neck and shoulders, perspiration (Wand: J 110 206 1938) It promotes stoeczematization in lichen chronicus simplex

Androgenic Substances.—Acneiform eruptions, hirsutism, enlargement of clitoris, and diminution in size of breast are physiologic effects of overdosage The acne is itchy and more common in women. See Greenhill and Freed (J 112: 1573, 1939); Geist and Salmon (J 117: 2207 1941) Acne from androgens is itchy; compare that from ACTH

Antabuse.—Tetraethylthiuram disulfide causes redness and burning of face and conjunctivae, rapid pulse pounding heart headache anxiety vomiting (Carver: BMJ 2 406, 1949) Acne (Barefoot J 147 1653 1951)

Antibiotics.—See individual antibiotics by name also moniliasis, etiology

Antihistamine Drugs.—Side reactions involving various systems including cutaneous have been reported, and rare fatal reactions were stressed by Wyngaarden and Seevers (J 145: 277 1951) Hemolytic anemia (Crumbley: J 143: 726, 1950) Common reactions: drowsiness, dizziness, headache insomnia, nervousness, nausea, impaired mental reaction. Fever cerebral edema, convulsions and nephritis are rarer Benadryl has caused urticaria

and eczema (Epstein: JID 1 : 161 1949); purpura (Deanie pers. comm.); dry mouth, ataxia, facial edema, sore tongue tinnitus (Geiger et al. J 133 392, 1947) Thephorin caused urinary retention (Uhle and Knoch: J 146 1319 1951) Diatrin and other anti histamines with benzamine linkage structure have caused agranulocytosis (Drake: J 14 4 1950) Pyribenzamine caused agranulocytosis (Blanton and Owens J 134: 454 194) urticaria (London and Moody: JID 13: 17 1949; Pratt: ADS 61: 667, 1950) rashes resembling pityriasis rosea and lichenoid dermatitis (Epstein: J 134: 782, 1947)

Antilepro1.—Chaulmoogra oil caused seborrheic dermatitis, fever and papular eruption (Brinkhaus: abs ADS 40 81, 1939)

Antimony.—Thiomalate for bladder schistosomiasis caused exfoliative dermatitis responsive to BAL (Ritter: La cet 1: 55, 1950) Neostam caused urticaria (Mathieson and Watson: J 11 209 1930)



Fig. 136.—Antipyrene-fixed eruption on dorsum f hand and knee region (Dr Robert V Andrade.)

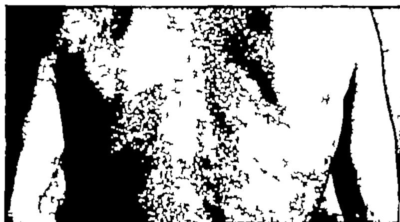


Fig. 137.—Arsenical pigmentation. (Drs. Fordyce and Ma Kee)

Antipyrine.—Usually morbilliform may be urticarial, scarlatiniform, or even bullous. Ma vol e muc membranes. Moderate itching Fixed eruption.

Antitoxin.—Immediate reactions sweating erythema, pruritus, urticaria, cough. Delayed reaction ccelerated serum disease n from 6 hours to 5 days. Serum sickness: urt caria, erythema, joint pains, malaise feve purpura lymphadenitis, albuminuria, leukope a. A ph lactic gangrene

Apiol.—Erythema, gingivitis buccal mucosal gangrene feve vomiting, n phritis (Lowenberg J 110 672, 1938)

Apresoline.—C used syst mic lupus erythematosus (q v) or syndrome much like it (Perry d Schroed J 154 670 1954; Muller et al J 157: 894 1955) Th drug gi to logy produced L.E. l ke disease and L.E cells (Wevs and Swift JAD 7 103, 1955)

Arsenic.—Erythematous, scarlatiniform, papula vesicula herpetic urticarial, keratotic pigmentary ulcerative even carcinomatous lesions. Palmar and plantar arsenical keratoses begin round the sweat follicles. Arsenical keratoses may improve unde large





Fig. 138.—Arsenical keratosis of palm. (Dr Louis P. Hamburger.)

Fig. 139.—Depigmentation and hyperpigmentation resulting from neoarsphenamine intoxication. (Dr Sam E. Sweitzer.)



Fig. 140.—Arsenical keratoses of soles. (Dr Sam E. Sweitzer.)

doses of vitamin A (Hall ADS 53: 154 1946) Arsenic trioxide produces an escharotic effect locally as well as erythema, weeping and scaling. Sensitivity to both trivalent and pentavalent arsenic may exist in one person. It is dangerous to give arsenic in any form to a patient sensitive to any arsenical. BAL yields remarkable improvement in all kind of arsenical intoxication (Eagle and Magnuson AMJS 30: 470 1946)

See Cancer etiology arsenic; also Hutchinson (TransPathSocLondon 39 352, 188) keratoses and cancer Osborne (AJDS 12 72, 193 16 3 1925) microchemical studies in arsenical dermatitis Harkwlale (A MMonth 6 392, 1946) arsenic in tobacco Pascher and Wolf (J 148 734 1952) pigmentation.

ARSPHENAMINES.—Erythematous, sea latiniform, morbilliform, and eczematous lesions followed by desquamation. Exfoliative dermatitis beginning in the flexures of the extremities, then on trunk and chest. *Sudden erythema 9 days after injection. Purpura*, hemorrhagic encephalitis, jaundice hepatitis. Ulcerative colitis, perforation. Acute yellow atrophy Agranulocytosis. Arsenical reactions of considerable severity may be expected perhaps once in 1 000 injections. Mapharsen is less toxic than other arsenicals and may be given to some patients even when previous intolerance has manifested itself; but if previously provoked dermatitis was severe no arsenical can be used without risking *disaster (Levin and Keddie J 115: 369 194_)*

The value of the patch test in determining sensitivity to arsphenamine is controversial, but a positive test before its administration is a contraindication. Recognition of earliest lesions or other evidence of intolerance is fundamentally important. Beerman and Stokes (AmJMedSci 201: 611 ...; 006, 1941) reviewed reactions and gave bibliography

Acetarsone causes the same troubles as other arsenicals, including dermatitis, jaundice, nephritis, fever and anemia (Epstein J 106 69, 1936) Myelitis, peripheral neuritis and fatalities were reported by Glaser (AmJDis Child 48 124 1934) Acetarsone pessaries caused exfoliative dermatitis, case (Peck BMJ 650 1951)

Acidic Arsphenamine—Unneutralized arsphenamine given intravenously kills within a few minutes, as a rule.

Nitritoid Reaction occurs at once or within 10 minutes, and is characterized by *suffusion of the face, sensations of asphyxia, even loss of consciousness. Epinephrine is the antidote.* Serious reaction may be prevented by cautious injection. It is rarely fatal.

Arsphenamine Collapse occurs at once. It is rare. Abruptly the patient becomes pale, pulseless, and breathless, and experiences agonizing pain in the kidney region. Atropine is protective, 1/150 grain being given by hypodermic 5 minutes before injection.

Shock is rare following the administration of arsenicals. Weakness, cyanosis, cold sweat, nausea, vomiting, collapse, syncope, fall in blood pressure, weakness and rapidity of the pulse, diminution of blood volume, rapid dehydration, increase in blood nitrogen, oliguria or even anuria occurring in progression. Not relieved by epinephrine, it may last for hours or days, and is dangerous but unpredictable. See Weinberg (AmJSyph 1 3 6, 1938)

Lichen Planus-Like and Pityriasis Rosea-Like Eruptions may occur (Goodman and Sullivan SouthMJ 36 491 1943)

Nausea and *Headache* frequently follow the injections. They are not contraindications to continuation of necessary treatment. Psychic influences are important in their cause and correction. At the time of injection, which should be given skillfully, the patient should not be hot, *hasty or exhausted, and he should have eaten a light carbohydrate meal perhaps two* hours previously

Herxheimer Reaction and *Therapeutic Paradox* see p. 448.

Arsphenamine Dermatitis is an absolute contraindication to the further administration of arsenic. I retain the remainder of these paragraphs with present tense and obsolete treatment (antibiotics and cortisone became available after they were written) because they illustrate what happened to medical science in the brief span of 15 years. Arsphenamine dermatitis presaged by itching and is characterized by macules or blotches sometimes confluent eczematous dermatitis on the face trunk and extremities. The patient should be questioned and examined before each injection. Arsphenamine dermatitis is treated with BAL and by complete rest soothing local applications, such as oatmeal baths *or aluminum acetate (1 500)* wet dressings, calamine lotion or Lassar's paste and sedatives such as aspirin. In the early stage sodium thiosulfate 1 gm. in 10 c.c. of water given each day intravenously may or may not be beneficial (Abramowitz et al. ADS 47 1 5, 1943) Epstein (*J 109 11 1937*) reported that all his patients with exfoliative dermatitis gave positive patch test reactions to neoarsphenamine. A course of heavy metal preceding arsenic seems to protect against the development of dermatitis, but if *given concurrently dermatitis is more likely to be severe*. In 80% the onset precedes the twelfth injection of arsenic. The recognition of itching palms, faint morbilliform rash in the antecubital areas, or itching or rash on the trunk, will prevent violent reactions or fatalities which would certainly follow the administration of more poison when mild symptom of poisoning already exist. The occurrence of coincidental allergic dermatitis is indication that arsenical should be temporarily discontinued. Furunculosis complicates many cases of *arsenical dermatitis this would not be so common if grease-free lotions* instead of ointments were applied for topical relief particularly in axillary and pubic regions. In treatment, Epstein gave (1) 1,000 c.c. 10% dextrose with 25 units of insulin intravenously daily (2) one gram sodium thiosulfate intravenously on alternate days *to 7 doses* (3) one gram calcium gluconate by mouth between meals t.i.d. (4) four grams sodium bicarbonate by mouth t.i.d.; (5) colloid baths; and (6) a high protein diet. Symptomatic therapy including the *administration of opiates when necessary* may be desired for each case. Glucose and saline intravenously help combat severe toxicity. Liver extract for intramuscular administration seems helpful, especially if hepatic damage is in evidence. Atropine and vitamin C have been recommended.

Erythema of the Ninth Day.—Morbilliform erythema of sudden onset but generally innocuous nature sometimes appears about the ninth day after a dose of arsphenamine. The rash appears on the trunk and limbs, spreads to involve the whole body, reaches its height in 24 to 48 hours, disappears usually within 3 or 4 days; it is accompanied by general lymphadenopathy and variable constitutional symptoms, including fever which falls when the rash fades (Epstein and Levin: AmJSyph 23: 490, 1939). While considered by some to be not a contraindication to further treatment, 14 cases of ninth day erythema in which arsenical treatment was promptly resumed suffered severe parenchymatous injury reported Leifer (AmJMSc 10: 458, 1945). See also Keim (ADS 31: 291, 1935), Peters (AmJSyph 25: 587, 1941); Beymann (AmJSyph 34: 468, 1950); Berlin (ADS 56: 771, 1947).

Hematopoietic Damage.—Neutropenia is the first detectable evidence of agranulocytosis due to arsenicals. Hemorrhagic purpura followed in cases which experienced varying degrees of shock following test doses (Falconer and Epstein: AIntM 63: 413, 1940), a fact suggesting that allergy was concerned. Thrombopenia, granulopenia and aplastic anemia occur (McCarthy and Wilson: J 99: 1557, 1932). Cases of bone marrow damage were reported by Kadin (ADS 37: 787, 1938), Schwartz and Von derHeide (J 128: 657, 1945); Fisher et al. (ADS 55: 57, 1947); Nelson (BMJ 1: 300, 1952). BAL may or may not prove helpful, but transfusion and penicillin are indicated.

Hemorrhagic Encephalitis occurs perhaps once in 5,000 patients on routine therapy usually after the second dose; the onset is within 1 to 144 hours after the dose with headache, vomiting, chills, fever, cyanosis, convulsions, coma, loss of sphincter control, mental changes, stiff neck, neurologic sign of encephalomyelitis. Death is the usual outcome. Pregnant women comprised 70% of 158 cases collected by Paley and Plewett (AmJS 23: 69, 1939). Massive dose and intensive methods have in the past carried a mortality approximating 1%, from this dread complication, wherein congestion, edema, focal necrosis, and capillary hemorrhages damage the central nervous system sometimes irreversibly (Boyd and Nie: ANeurP 49: 863, 1943). If recognized early by alert personnel, however, BAL successfully detoxifies (Eagle and Magnuson: AmJS 30: 420, 1946). Other therapy includes posture (the sitting position), administration of fluid and plasma, decompression by repeated lumbar puncture, control of hyperpyrexia, and sedation with paraldehyde (Ransome et al.: BMJ 1: 639, 1945).

Jaundice.—Impairment of liver function and significant drop in prothrombin indicate arsenical intoxication, yet discontinuation of treatment when these occur may not succeed in preventing serious complications, and vitamins B, C or K or liver extract neither prevent nor protect, so that massive arsen therapy should be abolished, according to Hinds and Kalz (AmJSyph 30: 70, 1946). The incidence and severity of hepatitis are not related to the total amount of arsenic given and histologic distinction cannot be made from epidemic or postarsam hepatitis, wrote Dibble and McMichael (BJVD 19: 102, 1943). Jaundice in syphilis thought due to arsenicals probably actually is infectious jaundice transmitted by faulty aseptic technic in treatment, in many instances (Marshall: BJVD 19: 52, 1943), although arsenical toxic hepatitis of course does occur and may be fatal. Syringe transmission of jaundice accounted for half of the cases reported by Willcox (BJVD 23: 121, 1947).

BAL.—See Treatment, BAL. Dramatic improvement in cases of arsenical dermatitis may be expected when the antidote is given early (Reeve: BMJ 2: 182, 1947) for urinary excretion of arsenic follows. Sometimes the patient fails to respond favorably (Peters et al.: Lancet 2: 497, 1947; Charleton et al.: QJM 17: 49, 1948). Thrombocytopenic purpura may respond (Schrampf: J 135: 1163, 1947).

Miscellaneous Arsphenamine Effects.—Gangrene from extravascular injection (Newman and Giles: OhioSMJ 36: 961, 1940). Myocarditis (Brown and McNamara: ADS 42: 312, 1940). Anuria from Mapharsen (Simon and Inlauer: AmJSyph 22: 612, 1938). Paralytic ileus with intestinal perforation (Dennie and Miller: ADS 35: 591, 1937). Keloidal bands and reticular atrophy of skin of neck (Epstein: ADS 37: 967, 1938). Rhinitis and asthma from inhalation of powder (Saunders: JAllergy 14: 70, 1942).

TRYPARSAMIDE.—Optic atrophy (135 cases studied by Mayer: J 109: 1793, 1937). Urticarial, eczematoid and fixed eruptions. Exfoliative dermatitis (Bragman: AmJSyph 18: 308, 1934). Delusions (Hoverson: AmJSyph 19: 217, 1935). Fixed eruption (Pillsbury: ADS 34: 163, 1936). General pruritus (Robinson: ADS 34: 231, 1936). Nitritoid reaction (Miller and O'Donnell: ADS 36: 304, 1937). Itchy papules on large trophic scar (Ellis: AmJSyph 22: 316, 1938). Erythema and crusting (Epstein: in YBD 1940, p. 159). Relapse of previous arsenical dermatitis (Franks and Fisher: ADS 42: 808, 1940). Visual and neural damage (Sloan and Woods: AmJSyph 30: 633, 1936; Kopp and Soloman: AmJSyph 24: 268, 1940; Bremman and Shaffer: BJVD 16: 148, 1940). Optic neuritis treated with BAL recovered (Friedenberg: J 135: 1072, 1947).

Arterenol.—Local venospasm and phlebitis; superficial vesicular eruptions and ulceration; ergotlike gangrene (Urlecchio et al.: J 152: 607, 1953). Necrosis of skin and vein arteriospasm and ischemic gangrene (Bufalco: J 152: 1654, 1953).

Aspidium.—Exfoliative dermatitis, vomiting, bloody diarrhea (Neumark: DWehn 106: 331, 1938).

Aspirin and Salicylates.—Urticaria, asthma, purpura, angioneurotic edema, laryngeal edema necessitating tracheotomy (Prickman and Buchstein: J 108: 445, 1937). Deaths (J 115: 1199, 1940). Allergy to aspirin is not frequent (Gordon and Blanton: AmJMSc 200: 390, 1940). Fatal thrombocytopenia (Rappoport et al.: JLabClinM 30: 916, 1945).

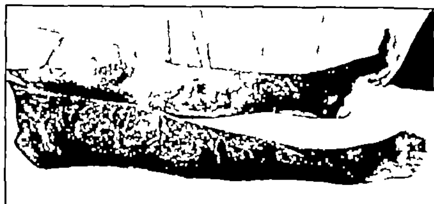


Fig. 141 —Arsenical dermatiti with gangrene, lue t neoarsphenamine. (Ronchese Am J Syph 15 348 1931)



Fig 142 —Barbiturate dermatitis due to Luminal. Miliary morbilliform, generalized (Drs Fordyce and MacKee)



Fig. 143 —Barbiturate caused this fixed eruption (Dr J Lama Callow y)

Asthma may develop after years of aspirin tolerance (Friedlaender and Feinberg: AnnIntM 26: 734 1947) Consider aspirin poisoning in presence of blotchy erythema of face profuse perspiration rapid breathing and tachycardia without distress cyanosis or pathologic signs in heart and lungs (Leveson BMJ 2: 628 1949) Urinary test for aspirin: boil to remove aceto acetic acid, add 10% ferric chloride drop by drop to 5 cc. urine white ferric phosphate turns purple if salicylates are present Treat by gastric lavage warmth, intravenous fluid, ACTH prevention of infection. See Walton and Bottomley (CanadMAJ 64: 187 1951)

Asterol.—Toxic encephalopathy convulsions (Wilson Hitch Featherston: J 150: 1002, 1004, 1006 1952)

Atabrine.—See Quinacrine

Atropine.—Erythema, scarlatiniform patchy or general rash, usually itchy; pyrexia, delirium, convulsions. May be hard to distinguish from scarlet fever See Scally (BMJ 1: 311 1936); Welbourn and Buxton (Lancet 2 11 1949) Dilated pupils, dry mouth, hot dry skin low white blood cell count helpful in diagnosis.

Aureomycin.—Mucosal and gastrointestinal irritation exfoliation of oral and anal epithelium, angular stomatitis, cheilitis, stomatitis, diarrhea pruritus ani, scroti or vulvae vaginitis, black hairy tongue, encouragement of monilial overgrowth, generalized erythema, vesiculopapular eruption urticarial erythema multiforme-like eruptions. See Behrman (J 144: 993 1950) Pareta (J 143: 652, 1950); Peck and Feldman (J 14 : 1137, 1950); Edit. (BMJ 1: 1104 1950); Gittell (J 14 1141 1951), shock Rlebes and Webb (ADS 64: 63, 1951), genital pruritus; Tomaszewski (BMJ 1: 888 1951) oral lesions resembling vitamin B deficiency Bedford (BMJ 1: 1429, 1951), asthma; Welsh and Goldberg (ADS 64: 256, 1951) fixed eruption; Kutscher et al. (JAllergy 4: 164 1953) stomatitis from troches.

Avertin.—Contains bromide See Bromides.

Aurothioglycanide (Lauron)—See Gold. Toxic in a fourth of patients treated erythema, pruritus, exfoliative dermatitis (Batterman: J 13 : 1013, 1953)

BAL may cause intoxication cramps tetany nausea lachrymation, salivation, burning sensations of mucous membranes, headache (Sulzberger et al.: JClinInv 25: 474 1946) These symptoms are considerably relieved by giving ephedrine 3 mg orally half an hour before an injection (Tye and Siegel: J 134: 1477, 1947) Abscess formation at the site of injection is common (Lancet : 497 1947) BAL has caused vesicular and bullous dermatitis in an arthritic woman intoxicated by gold (Hageman and Baghy: JMoMA 46 776, 1949) When given along with an arsenical it protects the spirochete as well as the patient from arsenical damage (DeOreo ADS 56: 605 1947) See Treatment BAL; Arsphenamine.

Banthine.—Exfoliative dermatitis (Clark and McNaughton ADS 66: 101 1953)

Barbiturates.—Exanthema with fever Urticarial, erythematous, bullous, ulcerous, eczematous or fixed eruptions. Pruritus, purpura, leukopenia, photosensitization. Exfoliative dermatitis (Winer and Baer: ADS 43 473, 1941) stomatitis and conjunctivitis (Mees and Long: ADS 46: 386, 1942); see Novy (CalifWM 43 324 1935) Light sensitivity leukopenia, purpura and death (Sweitzer and Lawson MinnM 20 92, 1937) Fatal exfoliative dermatitis (Wile and Benson: AnnIntM 13: 1243, 1940) Photosensitization (Stryker JMoMA 36: 484 1939) Bullous erythema and stricture of esophagus (Feldman ADS 46: 433, 1942) Purpura from Pentothal (Peterkin: BMJ 6 1946) from phenobarbital (McGehy and Bloomer AmJMed 14 600 1953)

Benadryl.—See Antihistamine Drugs.

Benzedrine.—See Amphetamine.

Bismuth.—Pigmentation of gums, ulcerative stomatitis, erythroderma papulosquamous erythema, scarlatinoid erythema, urticaria and pruritus Embolism nephritis, agranulocytosis, ulcerative colitis, argyria like pigmentation, arthralgia, jaundice. Brittingham (JMAGa 22 322, 1933) showed that stomatitis is of high incidence in persons with caries or pyorrhea. Salivation pain and swelling of tongue gastric upset with watery diarrhea and griping renal irritation with frequency weakness, malaise, albuminuria (even anuria) headache backache and malaise similar to influenzal symptoms except the lower fever — all these occur bismuth poisoning Ninth day erythema (Grand ADS 41: 1076 1940) Arterial embolism (Sulzberger and Baer AMJSyph 24: 50, 1940; Underwood ib. 29 656, 1945) Oral manifestations (McCarthy and Dexter NEngJM 213: 345, 1935 not in edentulous mouths; Felsher and Jones: JID 4 135, 1941 keep mouth clean with 15% sodium hexamet phosphate in tal when on bismuth therapy) Stomatitus and albuminuria like lead poisoning (I ters: AmJSyph 26 84, 1942) Response to BAL (Reekie: BMJ 2: 1218, 1949) Hepatitis (Kolchar and Reynolds: J 120: 848, 1942) Arthralgia (Gonner ADS 34 233 1936) Renal damage (Keith and Osterberg AIntM 60 416, 1937) Pityriasis roseaike eruption (Dobes and Allen: SouthMJ 4 672, 1949)

Bistrimat stomatitis and dermatitis (Wirth: ADS 60 1206, 1949) sore face, bleeding gums, vesicular stomatitis (Noun and Greenhill ADS 59 347 1949)

Bismarsen has caused arsenical dermatitis and purpura (Swartz et al.: ADS 33 874 1936)

Boric Acid.—Accidentally given by mouth, this is poison, causing gastroenteritis, hepatitis, nephrosis, cerebral edema, and exfoliative dermatitis (Young et al.: CanadMAJ

61 447 1949) Percutaneous absorption can cause fatal poisoning (Watson: J 1*0: 332 1945) Dusting powder has caused toxicity by transcutaneous absorption (Brooke: GP 7: 43, 1953; Maxson: KyMJ 5_ 4*3 1954 Ducey and Williams JPediat 43: 644 1953)







Figs 144 145, and 146 —Art rial embolism following accidental intra-arterial injection of bismuth in oil into i ferior gluteal vessel. Fig. 144 show dry gangrene and beginning separation of slough on fifteenth day Fig 145 shows spontaneou separation of slough, granulation and partial healing seen on the ixty-ninth day footdrop present from destruction f sciatic nerve. Fig 146 hows sca many months later (DeWolf UCutRev 37 423 1932)







Fig. 14 —Bromide eruption. (Dr F Ronchese)
Fig 148 —Bromid eruption. (Dr Sam E Sweitzer)
Fig 149 —Vegetative bromide eruption f leg.

Bromides.—Fairly common from sedatives and headache remedies. Lesions develop slowly and re persistent. Erythem tous, urticarial pustul r f runcul r condylom form bullous, and squamous. Eruption localized or ge ral. Hemorrhagic, fungating lesions, erythema odosumlike, toxic psychosis common. Treat by rging qua t ties f sodium

chloride and water and sodium chloride solution intravenously; or by intravenous sodium chloride solution, continuously by drip, with continuous suction of gastric juice from the stomach (Furniss BGO 63: 118, 1939) No relation is found between blood bromide level and skin lesions (Kimberly: JID _: 331, 1939) Serum bromide is reduced by mercurial diuresis (Hussar and Holley: AmJMedSci 223 202, 1952) Ammonium chloride is a better diuretic than sodium (Cornbleet: J 146: 1110, 1951)

Bromoderma limited to sites of insulin injections (Abramowitz ADS 40: 478, 1939) Mental symptoms (Skoog: JMoMA 36 339 1939 Cunningham: BMJ 2 226 1946, 3 rashes among 88 intoxications) From B.C. Headache Powder (Krack and Platt J 126 107 1944); from Asertis (Robinson: Practical Dermatology Blakiston, 1939) Fixed eruption, erythematovesicular (Tolmach and Frank: JID 12 41 1949) Infant with rash from mother's milk (Young BMJ 1: 769, 1930) Nicotinamide appears to prevent and to cure bromism (Feinblatt and Ferguson: NYSJM 52: 2017 1952)

Bromsulfalein.—Urticaria, and fixed eruption at site of accidental intradermal injection (Sievers et al.: JAllergy 20: 167 1949)

Carbarsone.—See Arsphenamines, acetarsone.

Carbromal.—Bromi e-containing drug resembli g Sedormid, causing purpura, 6 cases (Borrie: BMJ 1: 645 1953)

Chloral Hydrate.—Papular lichenoid, urticarial, purpuric, erythematous, and scarlatiniform. Bullous, exceptionally



Fig 150.—Dilantin hypertrophic gingivitis (Dr J Lamar Calloway)

Chlorpromazine (Thorazine)—Agranulocytosis (Prokopowycz J 157 1041 1955) jaundice, agranulocytosis, L.E. like rash and symptoms (Hodges and LaZerte J 158 114, 1955) Maculopapular rash, nonrecurring (Margoli et al. AD : 72, 1953)

Chloroform.—Erythematous or purpuric.

Chloromycetin.—Angioneurotic edema and shock (Patterson: NoWM 40: 352, 1950) Glossitis, cheilitis, pharyngitis, burning mouth, maculopapular rashes (Altemeis and Culbertson J 145: 449 1951; Ursdek et al. ADS 64: 217 1951) Bone marrow hypoplasia, aplastic anemia (Rich et al.: AnnIntM 33 1459 1950 see J 149 231, 912, 1293, 1801 1952) Review of 639 blood dyscrasias, 55 on this drug only 23 deaths (Lewis t al. Antibiot&Chemother 2: 601, 1952)

Chloroquin.—Pruritus toxicity rare (Loeb et al. J 130 1069, 1946) nausea, loss of weight, lichenoid dermatitis (Alving et l JClinInv 27 66 1948 Goldman et al.: J 153: 1428 1953) Restlessness, confusion, diplopia, cumulati e toxicity Pruriti burni g eruptions, erythematous, discrete and conflue t, xt sive (Ayres and Ayres J 157 186 1955)

Cinchophen.—Angioneurotic ed ma, erysipelatous swelling of face, pruritus, scarlatiniform rashes, jaundice, death (Palmer and Woodall J 107 760, 1936)

Cod Liver Oil.—Acneif rm.

Codeine.—Erythema with pruritus, sometimes follicular or perifollicular and scarlatiniform (Seldmann ADS 47 654, 1943) Exfoliative derm titis (Moyer: NEngJM 238 409 1948); desquamation (MacK nzie BMJ 766, 1949; 2 231, 1951)

Cortisone.—See ACTH, but cortison is a safe drug from the standpoint of cutaneous changes. While it causes sod um retention, t seldom, in my experience causes acne hirsutism, pigmentation etc. See Boland and Headley (CalifM 74 416, 1951); T ylor et al. (J 144: 1059 1950); Smith et al. (ADS 67: 620 1953) acne in infant.

Cyvarine.—Exfoliative dermatitis; alopecia (Levin and Bahrman: J 115: 41 1942).

DDT.—Dependent and flexural erythema, papules and purpura (Stryker and Godfrey: JMoMA 43: 384 1946) See Dermatitis Venenata, insecticides occupational hazards (Gordon BJIndustM 3: 245 1946); toxicology (Council Rpt. J 145 728 1950)

Diasone.—Blood dyscrasia Red, maculopapular rash with enanthem, becoming vesicular (Pfuetze and Pyle: J 125: 354, 1944) Dermatitis, lepra reaction, erythema nodosum (Reyes et al.: ADS 59 118 1949; Combes and Scott ADS 66: 748 1952)

Dicumarol.—Alopecia in 11 of 87 patients on anticoagulant therapy for 6- 4 months (Fisher et al. SchweizMWehn 83: 509 1953) I saw a ra h resembli g purpura annularis telangiectodes Local hemorrhage and necrosis of skin (Verhagen ActaMScand 148 453, 1954) ACTH dimini hes anticoagulant effect.

Digitalis.—Erythematous and papular followed by desquamation. Digitoxin caused thrombocytopenic purpura (Berger J 148 282, 195_)

Dilantin.—Oral changes resembling scurvy (Kimball: J 11_: 1_44 1939) Hemorrhagic erythema multiforme (Ritchl and Kolb: ADS 46: 856 194_) Pruritus, scarlatiniform rash, bullous mucositis at body orifices (Ellis: SouthMJ 36: 575 1943) Hypertrophy a d overgrowth of gums (McCarthy: ADS 45: 4*7 194_) Fixed eruption (Barton and O'Leary: ADS 48: 413, 1943)



Figs 151 and 152.—Gold sodium thiosulfat caused this case of exfoliativ dermatitis (Dr Robert Andrade)

Dinitro-orthocresol.—Weed kille with cumulative toxicity from inhalation, causing yellow pigmentat on of kin hyperhidrosis, weakness, loss of weight, hemorrhage l lungs (Bidstrup and Payne BMJ 16 1951)

Dinitrophenol.—Urt aria, purpura, pruritu , acroerythema (Koun ADS 33 288, 1935) Exfoliati e dermat t s, cataract, polyneuritis (Hitch a d Schwartz: J 106 130 1936) Leukopenia and purpura (Imerman and Imerman J 106: 108_ 1936) See Simkins (J 108 117 193, 193)

Diodrast.—Urt caria and wheezing from intravenous pyelography (N terman and Robins J 119 491 194_)

Diphenylhydantoin Sodium.—See Dilantin.

Epinephrine.—Gangrene (Cohen and Waterstone JAllergy 11 393, 1940)

Ergot.—Po soni g from ergoted grain (Gabl et al. BMJ 2 630 1951) symptoms in 6 to 48 hours, depression, nguish, nausea, bell pain, sense of pharyngeal tightness paroxysmal h pe hidrosis, pallo low pulse cold ext emit es, burning pains in intestines and some col pat ent pale limp, n ble to focus eyes f reading paresthesia, cramps, fainting spells death with muscle spasms and cardiovascular coll pse. Ergotamine used medicinally m cause gangrene relief with papaverine (Perlow and Bloch: J 109; 27

1937) See v Storch (J 111: 291, 1938); safe in 0.5 mg dose twice in 1 day in 1 week, if obliterative vascular disease is absent. Flexural urticaria and follicular dermatitis resembling lichen spinulosus (Lindsay ADS 48: 134, 1943)

Estrogenic Substances.—Purpura (Watson et al. JLabClinM 3?: 600, 1947) See Stilbestrol.

Fixed Eruptions.—Erythematous, swollen and bullous plaques followed by pigmentation suddenly recurrent in the same places with each dose of the drug have resulted from antipyrine phenolphthalein barbiturates, cinchophen, mercury quinine acriflavine acetyl arsan, Mapharsen, Tryparsamide. Early the eruption is urticarial, eczematous, and pruritic (Abramowitz ADS 43: 07? 1941) Phenolphthalein (Abramowitz: ADS 40 436, 1939) Arsphenamine (Chargin and Leifer: JID 3: 443, 1940) Magnesium hydroxide (Abramowitz and Russo: ADS 41: 707 1940) Sulfonamide (Meltzer: JID 13: 13, 1949) All drugs known to cause fixed eruptions listed by Cornbleet et al: (AD 71: 507 1955); phenolphthalein cases rare; alleged cases should be given test doses.

Fluoride.—Follicular pustules mottled teeth (Gaul: ADS 36: ?6 1937)



Fig. 161—Atrophy of fat, following injections of insulin in a diabetic. (From Clendening and Hashinger Methods of Treatment, Mosby ed. 7 1941.)

Frei Antigen.—Papular eruptions. Fever Flaccid paraplegia ranging from mild to fatal (Keim and Wakefield: ADS 40 709 1939) Erythema nodosum (Sonck; abs YBD 1940, p. 180)

Gold.—Gold sodium thiosulfate, succinimide, Sanocrysin, may produce erythema, morbilliform eruptions, leukopenia stomatitis exfoliative dermatitis, urticaria, ephritis, jaundice, purpura. Argyria-like pigmentation (chrysocyanosis) especially about eyes. Pityriasis rosea-like (Wile and Courville ADS 42: 1105, 1940) Pigmentation (Schmidt ADS 44 446 1941; Sezary et al. BSocfrançD 40 1613, 1933) Dermatitis frequently associated with positive patch test, test sometimes positive before dermatitis appears (Lichtenstein: JAllergy 6 460 1935) See Phillips (NEngJM 214 114 1936) Treatment with BAL effective (Cohen J 133 749 1947; Simpson BMJ 1 545, 1948; Sulzberger ADS 60: 807 1949) ACTH more effective than BAL (Stenberg and Roodenburg J 146 1225, 1951) Cortisone is effective. Thrombopenic purpura responds better to BAL than to ACTH (Thompson BMJ 1 899 1954)

Heparin.—Urticaria, erythema, fever; itchy eyes, nose and mouth controlled by ephedrine (H ck et L PSEBMC ?? 165, 195_)

Hexamethonium Bromide.—Rosacea from bromide (Sommerville and Allen: BMJ 1 864, 1951)

Hexamethylenamine.—Urticaria, erythema.

Hydralazine.—See *Apresoline (lupus erythematosus)*

Insulin.—Urticaria, symptoms like serum sickness (Baver: J 102: 23 1934) Lipoma told lesions (Adlersberg: MedKlin 31: 779 1935; Bader and Vero: JPediat 10 184 1937) Local atrophy of fat at sites of injections (Rosenberg and Berliner: WienKlinWchn 49: 1.53 1936; Yohalem and Pollack: JMtSinaiH 15: 320 1949) Desensitization of urticarial case (Weitz: JAllergy 14: 220 1943) See Gouldner and Ricketts (JClinEndocrin *: 505 194.) Local urticaria with passive transfer (Musso and Golay: Dermatologica 109: *74 1934)

Iodides.—Erythematous purpuric urticarial acneiform, papular nodular pustular bullous, carbuncular and vegetating Fatal hemorrhagic vegetative and ulcerative dermatitis. Lachrymation salivation red nose Sites of predilection are areas richest in sebaceous glands—face shoulders and back—although no region is exempt. The lesions





Fig. 184 —Purpuric iodide eruption in a nursing infant whose mother took iodide. (Dr D Wood Ruggles.)

Fig 185 —Iodism following diagnostic use of Lipiodol (Dr D. E. H. Cleveland)



Fig 186 —Iododerma, a fatal case showing vegetating and hemorrhagic lesions (Goldstein J 106 1469 1936)

may be discrete or confluent, and there may occur suppuration and ulceration, eventually scarring The eruption generally appears promptly, within 24 48 hours, but it is usually persistent. Intravenous sodium thiosulfate checks reaction from potassium iodide given orally to an iodine sensitive person. Persons with cardiac or renal embarrassment are susceptible (Wartzk MJAustral : 38 1933) Purpura (Davis and Saunders ADS 53: 645, 1946) Bullous (Adamson BJD 50 167 1938) Fungating (Cleveland Canad MAJ 30: 131 1934 Hollander and Fetterman ADS 34 228 1936 Pi kus et L JMich SMS 43: 709 1943) Fever (Katzenst n AmJSyph 22 348, 1938) Absorption from vagina (Schoch J 104 85., 1935) Iodized salt and odism (Bechet JID 8: 400 1947) Lipiodol (Belot J 89 892, 1927 Readding BMJ 114 1934) Diagnostic radiologic iodized chemicals (Irwin AnnOtol 61 403 1952) Rash coryza and fever in hyper

thyroid patients treated with iodide (Barker and Wood: J 114: 1029 1940) Response to ACTH in vegetative case with extreme eosinophilia which followed pyelography and post operative iodide in asthmatic undergoing prostatectomy (Cape: BMJ 1: 255 1954) Nicotinic acid, 25 mg s.c., counteracts iodide aggravation of acne (Barefoot: AD 1: 529, 1955)

Iodoform.—Macular purpuric papular vesicular

Isoniazid.—Pruritus legs and head, desquamation of hands and body (Connell Rpt.: BMJ 1: 737 1952) Pellagra (McConnell and Cheetham: Lancet 2: 959 1952) Burning formication sensations of smothering, lancinating pains in hand and feet (Pickroth: abs J 153: 771 1953)

Karaya Gum.—In some hand and hair lotions, laxatives, gumdrops, this has caused atopic dermatitis, asthma, urticaria (Bullen: JAllergy 5: 484 1934; Figley: J 114: 74 1940); pigmentation like phenolphthalein (Bowen: ADS 39: 506 1939)

Khellin.—Urticaria, dermatitis, nausea, dizziness insomnia from Visammin (Roseman et al.: J 143 160 1950)

Lipiodol.—Iodism; see Iodides.

Liquorice.—Plaques of fixed eruption tending to bulla formation (Korting and Unselt DermWchr 123: 29 1951)

Liver Extracts.—Urticaria, erythema, asthma, pruritus, nausea, weakness (Crisp: J 110: 506 1938; Krantz: ibid p 807; Feinberg et al.: AnnIntM 18 311 1943) Local histamine-like reaction, erythema and swelling (Englehardt and Derbes: SouthMJ 37: 31 1944) Allergy to pork not beef liver (Bauer et al. NEngJM 236 622, 1947)

Mandelic Acid.—Violent punctate erythema with swelling of face and extensor skin and ebemosis (James: BMJ 1: 1455 1937)

Mercuprin.—Urticaria, mercurial rashes, fever asthma; reaction more likely when kidneys are severely impaired already (Gottlieb: AnnAllergy 6: 519 1948) BAL effective antidote (Long and Farah: Sci 104: 220 1946)

Mercury.—Erythema pruritus, scarlatiniform with exfoliation; salivation, stomatitis, gastroenterocolitis. See Pink Disease Review of fatalities (Wolfenstein: BerlKlinWchr 1004 1913) Arterial embolism (Carley: VDI 17: 281, 1936) Dermographia, hyperhidrosis, weight loss, insomnia, tremor in hatters fur cutting industry (Neal and Jones J 110: 337 1938) Cinnabar tattoo caused general erythema (Novy: ADS 49: 172, 1944)

Mesantoin.—Macular rash, fever eosinophilia, stupor granulocytopenia; fatal bullous exfoliative dermatitis (Ruskin: J 137: 1031 1948) Pancytopenia (Frank and Holland: J 139: 1148, 1949) Pigmentation (?) (Hunter and Jenkins: J 147: 744 1951) See Bercel et al. (J 143 1460 1950) Compare Dilantin.

Methimazole.—Rashes, agranulocytosis, arthritis, toxic hepatitis, peripheral neuritis (Acetta et al.: J 155: 253, 1954)

Morphine.—Erythematous, maculopapular vesicular urticarial. Pruritus.

Nalorphine (Nalline).—Sweating and other symptoms of abstinence from opiates in addicts, not in normal persons (Edit.: J 154 414, 1954)

Nicotinic Acid.—See Vitamins.

Paludrine.—Erythema, swelling of hands and feet followed by exfoliation; urticaria pruritus (Findley quoted by Loewenthal: BJD 64: 106, 1952)

Para-amino Salicylic Acid.—Scarlatiniform or morbilliform rash, fixed eruption, fever; nausea, diarrhea, lymphadenitis, hepatitis, nephrosis (Kierland and Carr: PSMMC 24: 539 1949 Steel: BMJ 1: 415 1952) Lichen planus-like eruption after several months (Shatin et al. JID 21 135 1953) Thrombocytopenia (Wurzel and Mayock: J 153: 1094, 1953)

Penicillin.—Reaction resembling serum sickness (Gordon: J 131: 727 1946) Vesiculation with or without spreading scarlatiniform eruption of toes, feet, crotch (Lamb: ADS 52: 93, 1945) Pompholyx. Herxheimer-like phenomena, and aggravation of bacterid (Heinlein et al.: USNMBull, April, 1946) Oral administration frequently provokes urticaria. Universal erythema perhaps with dependent petechiae. Erythema multiforme-like eruption, spreading from the dermatosis for which penicillin was administered Erythema nodosum with superimposed bullae Dermographia without urticaria (Kalz: ADS 54: 66 1946) Exfoliative dermatitis (Nolan and Pedigo: AnnIntM 25: 725 1936) Pityriasis rosea-like (Epstein: J 134 782, 1947) Agranulocytosis (Spain and Clark: AnnIntM 25: 732, 1946) Topical application eczematous dermatitis; flares of this may occur if subsequently penicillin is given parenterally (Templeton et al. ADS 56 325 1947); urticaria (Kalb J 145 1004 1951); see Black tongue.

Sensitization related to T. gypseum infection (Cormia and Lewis JID 7 375 1946), not related (Peck and Siegel ib. 9: 165, 1947)

Passive transfer test negative in penicillin urticaria (Callaway and Barefoot: JID 7 43 1946) Reaction rate about 9% commonest urticaria epidermal sensitization easy to induce (Gottschalk and Weiss ADS 53: 4, 1946) Classification of reactions see Farrington et al. (BMJ 41 614 1948) Exfoliative dermatitis (Shaffer: NEngJM 238 660 1948) Spontaneous sensitivity in 5%; 10% of those receiving penicillin got reactions, mostly males probably due to previous time (Peck et al. J 138: 631 1948) Stomatitis and glossitis from oral tablet (Goldman and Farrington: ADS 57: 399 1948; Crowe BMJ 1 171 1949)

Intramuscular injection of beeswax and oil (Bondy et al.: AmJM 3: 34, 1947) Injection damaging peripheral nerve (Broadbent et al.: J 140: 1008 1949) Purulent abscesses at sites of injection (Call and Gilbert J 134: 1476, 1947) Eczematous reaction

to procaine fraction (Peck and Feldman: JID 13: 109 1949) Beeswax allergy (Watson: BMJ 1 601 1945) Sensitization to instillation in maxillary sinuses (Everett: J 146: 1314 1951) Vesicular dermatitis of hand showi g only tuberculin type reactivity (Epstein and Pinku : AnnAllergy 4: 136, 1946) Fixed eruptions (Canizares: ADS 63: 500 1951) Reviews: Farrington (SouthMJ 48 637 1955); Strauch et al. (TexasSJM 50 699, 1954)

Serum sickness type of reactions showed marked depression of hemoglobin (Riley: ADS 65: *7 1952) Fatal exfoliative dermatitis not necessarily due to penicillin (Hase lck: J 143: 116, 1949) Acceleration of blood clotting (Macht: J 143: 205, 195_). Granulomatous visceral lesions, fatal (Waugh AmJPath 28: 437 1953) Hazards (Gilman: USArmedForcesMJ 1: 1153 1950) Allergic hydroarthrosis, serum sickness, anaphylactic shock (Suchecki: BMJ 2 938 1946) Anaphylactic shock (Sterling: JAllergy *4 54_, 1953) Skin test are unreliable in predicting penicillin allergy (Berger and Eisen J 150: 191 1953)

Anaphylactic death (Higgins and Rothschild: NEngJM 4 : 644 1952; Felsberg et al.: J 15_: 114 1953 Pick and Patterson BJD _ 605 1953; Prior and Burrell South MJ 46 11 1 1953; Edit BMJ : 0 1953)

Desensitization (O Donovan and Klorfajn: Lancet : 444, 1946 Peck et al.: J 134: 1546 1947; Alexander: ADS 63: 333, 1953)

Treatme t antihistamine drugs intravenous procaine (Dressler and Dworki J 133: 849 1947) *ACTH (Lichtenstein and Friedman: J 147: 1633 1951)* cortisone; intravenous calcium in erythema nodosum type Aluminum acetate or permanganate baths.

Pertussis Toxin.—Thrombopenic purpura (Kugelmann: J 10? _120, 1936)

Phenacemide (Phenurone).—Rashes, exfoliative dermatitis (Tyler and King: J 147: *17 1951*)

Phenacetin.—Urtic ria, erythema.

Phenergan.—Photosensitization followed topical application (Tzanck et al.: AnndeD 8: 433, 1951)

Phenindione.—Rash, jaundice anemia (Makous and Vander Veer: J 155: 739 1954)

Phenolphthalein.—Persistent spots pink, dusky red, itchy sometimes bullous during flare fading to leave persistent brownish purple stains; fixed eruption. Stomatitis, catarrhal col t Common ingredient of laxatives. Pigment is melanin (Wise and Abramowitz ADS 5 297 192_) Urticarial lesions, co junctival ecchemoses, mucosal ulcers, scaly erythroderma, erythema multiforme-like eruptions, nephrosis, visceral hemorrhage ul erati e lti (Newman J 101 61 1933) (?) blu stain of nail bed (Campbell: BJD 43 186, 1931) Tra splantation experiments: normal skin moved to affected site reacted (Wise and Sulzberger: *7 549 1933) Bibliography and review (Abramowitz: ADS 31: 7", 1935) Toxicity (Knowles et al.: ADS 33 2?7 1936); drugs containing phenolphthalein (Belote and Whitney ADS 36 *70 1937); effects on kidneys (Fantus and Dyniew ex J 108 439 1937); on intestines (Soper: AmJDigestDis 5: 297 1938)

Phenylbutazone.—Macular erythema morbilliform, vesicular papular, purpuric and rt carial eruptions (Kuzell et al. J 149: 29 195 ; Stephen et al.: J 150: 1084, 1952; Ste brocker et al.: ib. p. 1087) Exfoliative dermatitis (Cheret and Siegel J 151: 556 1953 Fishman and Reynolds J 153: 64_, 1953) Fatal bullous erythema multiforme (Cone et al. ADS 69: 674 1954) Agranulocytosis (Stifel and Burnheimer: J 151: 555, 1953 see p. 53) agranulocytosis helped by ACTH (Werblow and Neber: J 151 1256, 1953)

Phenytoin Sodium.—See Dilantin.

Photodynamic Effects of Internally Absorbed Drugs.—See Hydroa; Phenergan; also Mathews (APath 23 399 1937)

Pituitary Extracts.—Angio eurotic edema (Simon and Ryder J 106 515 1936) Urti aria from posterio pituitary (McMann J 113 1488, 1939) Collapse (Seligman: J 114 344 1940) See also ACTH.

Presidon (Pyrithyldione).—Ulcerative stomatitis, proctitis, vul itis; agranulocytosis (Co er and Halpern NEngJM 4_ 49 1950)

Promin.—See Sulfonamides.

Pyribenzamine.—See Antihistamine drugs.

Quinacrine (Atabrine).—See also Lichen planus; lupus erythematosus; Chloroquin. Y llow pigmentat universal but more intense on exposed parts (Sugar and Waddell BMJ ?9 _34 1946) Blue macules o face, nose nd mucosae. Blue nails (Sugar and Waddell BullUSAMD 4 370 1945) Rarely hepatitis, exfoliative dermatitis (Agress J 131 14 1946) Fluoresce greenish yellow of all hair and skin (Glasberg and Shallenberger J 131 80* 1946 Kierla d et al.: ib. p. 809) Color plates of blue pigme tation (Lutterloh nd Shallenberger: ADS 53: 349 1946) Fatal aplastic anemia, from 0 1 Gm. B.I.D (Parm and Sawitsky: J 153 1172, 1953); from 8 0 Gm. in 55 days (Vilanova d d M raga A d D 80 360 1953)

Quinidine.—Edem scarlatiniform, pruritic, general o scattered rashes, often located on dependent part Purpura, thrombocytopenia (Nudelman et al. J 137: 1219 1948; Moodie BMJ 563 1950); mechanism of cause of purpura, allergi interference with clot retraction in presence of sensitive serum and the drug (Larson Blood 8: 16, 1953) Fe e (Be ley and Saland J 148 1131, 1952) Exfoliative dermatitis (Taylor and Pota hnick: J 145 641 1951) eruption resembling lichen planus (Wechsler ADS 69: 41 1954)

Quinine.—Erythematous, scarlatiniform, purpuric, urticarial vesicular bullous and ulcerative attended with severe itching Acuminate follicular papular pruritic eruption. Bullae on hands and tongue (Settle: J 106: 1801, 1936) Coppery rash fatal anuria (Vartan and Discombe: BMJ 1: 625, 1940) Thrombocytopenic purpura (Bolton and Young: JClinPath 6: 320, 1953; Steinkamp et al.: JLabCli M 45 18, 1955) Anacin contains quinine (Lamb: ADS 40: 803 1939) and Bromoquinine does also.



Fig. 157.—Phenolphthalein eruption in a young man, who had been taking the drug over a period of many months.



Figs 158 and 159.—Phenolphthalein stomatitis in 2 patients. Fig. 158 shows glossitis in the form of a fixed eruption. Fig 159 shows exudative cheilitis. (Dr Belford Shelmire.)

Radium.—Mandibula destruction; sarcoma (Evans and Aub AIntM 11: 1443, 1938)

Reserpine.—Depression, arthralgia, stuffy nose. I have seen several cases of diffuse alopecia from it.

Rutin.—See Vitamins.



Fig. 160 —Bullous erythema multiforme from phenolphthalein



Fig. 161 —Phenolphthalein intolerance. (Dr J Lamar Callaway)

Salicylates.—See Aspirin. Erythema; scarlatiniform, morbilliform, urticarial, vesicular bullous, rarely ulcerative eruptions. Thrombocytopenia, purpura. Percutaneous fatal intoxication (Young: SouthMJ 45: 1073 195.)

Sclerosing Agents.—Emboli are less common since coagu ants are less used. Sodium salicylate may cause urticaria. Quinine (q.v.) Sodium morrhuate (q.v.) See Shelley (J 112: 1792, 1939)

Sedormid.—Allyl isopropyl acetyl carbamide causes thrombocytopenic purpura (Boas and Erf: NYSJM 36: 491, 1936; Hoffman et al.: J 110: 725 1935; Moody: ib. p. 726; Hill: J 111: 1450 1938; Huber: J 113: 674, 1939; Falconer and Schumacher: AIntM 65: 122 1940) Thrombocytolysis in vitro (Ackroyd: ClinSci 7: 231 40; 8: 235, 269 1949) Temporary intolerance (Grant: BMJ 2 128 1953)

Selenium.—Erythema and edema of exposed parts, porphyria and leukocytosis with relative lymphocytosis (Halter: abs YBD 1939, p. 546)

Silver.—*Argyria* is permanent discoloration of the skin which sometimes follows prolonged administration of silver salts, particularly silver nitrate May result from use of Argyrol or silver arsphenamine. Earliest signs of pigmentation are noted on the edges of the gums. The hue of the affected skin ranges from a bluish or bl ish gray to a slate or bronze color and may be generalized or localized to treated area. Color simulates that of cyanosis from heart disease (Smith and Watson GlasgowMJ 35: .5 1954) The deposit of silve or rather the silver combination is limited to the margin of the connective tissue and affects particularly the elastic fibers and the sheaths of the membranes (Hill and Mo tgomery: ADS 44: 588 1941) Many elastic fibers are sheathed with the metal. Stillians and Lawless (J 9?: ?0, 1929) successfully bleached the pigmentation by injecting locally a mixture of 1% potassium ferricyanide with 6% sodi m thiosulf te.

See Gaul and Staud (ADS 30 433 1934 J 104: 1387 1935) spectrometric nalysis Harker and Hunter (BJD 47: 441, 1935) occupational rgyria in silversmiths; Stillians (ADS 35 67, 1937), review; Hill and Pillsbury (Argyria The Pharmacology f Sil er Williams nd Wilkins, 1939); Levin and Smith (NEngJM 226: 482, 1942) confusion with heart disease Olcott and Riker (Sci 105: 67 1947) DAL futile in rats Rosenthal and Ollswang (ADS 57 742, 1948) DAL futile in human beings.

Sodium Morrhuate.—Pruritus, erythema, edema, flare at sites of previous injections. Urticaria, collapse. Embolism. (Shelley: J 112: 1792 1939)

Stilbamidine.—See Blastomycosis, treatment.

Stilbestrol.—Edema of legs, erythema progressing to exfoliati e dermatiti (Keyser: ValMMonth 69: 544, 1942; Kasselberg: J 120 117 1942) Hypertrophy of breasts (Dunn: J 115: 2263, 1940)

Stovarsol.—See Arsphenamines, acetarso e.

Stramonium.—Contains atropine, scopolamine, hyoscyamine; flushing, dry erythema, scarlatiniform rash dilation of pupils (Hughes and Clark: J 11.: .500, 1939)

Streptomycin.—Histamine-like flushing headache, fever myalgia, and arthralgia. Maculopapular and erythema nodosum-like exanthems (Hettig and Adcock: Sc 103: 355 1946) Rashes resembling erythema of ninth day not a contra dication to furthe dosage (Steiner and Fishborn: ADS 56 511, 1947) Contact dermatitis (Strauss and Warring: JID 9 3 90 1947) Severe membranous stomatitis (Beham nd Perr J 135 493 1948) Deafness, dizziness, leukopenia, anemia, renal irritation (Davis et al.: AnnWest M&S 2: 45 1948) Erythema nd stomatitis, fatal (Pallister BMJ ?: 1?71, 1949) Exfoliative dermatitis (Lindars and others: Lancet 1: 110, 112, 233, 234 1950) Hypertrichosis n children (Rouques PresseMéd. 58 1230 1950) Purpura (R densky and Fisher: J 147 311 1951)

Sulfisoxazole.—Agranulocytosis responsive to ACTH (McCluskey: J 152: 232 1953)

Sulfocyanate.—Erythema, papular rash, exfoliative dermatitis (Baker and Brunsting J 108 549, 1937) Toxic alopecia, perineal pru t s mucosal petechiae (Holla d et al.: ADS 59: 112, 1949)

Sulfonamides.—Erythema with edema, urticarial followed by desquamation. Scarlatiniform. Tends to localize on parts exposed to sunlight; photosensitization. Erythroderma. Pruritus, granulopenia purpura. Cyanosis. Methemoglobinemia. Porphyrinuria. Acute yellow atrophy Headache, nausea, insomnia; worse with sulfapyridi e. Erythema nodosum like eruptions. Eczem tous flare of exudative derm titis for which drug was given, with development f widespread eruption more or less resembl ng the original disease (Livingood and Pillsbury: J 121 406 1943) Conjunctivitis and f ver Pemphigoid eruption (Joh son J 1 4: 979 1944) Fixed eruption (Dostrovski and Sagher: ADS 49 418 1944) G neral erythema, conjunctivitis and purpura, fatal (Gessler BMJ 37 465 1944) Peripheral neuritis. An ria. Topical use often sen itizes, so that subsequent i ternal administration causes sensitization phenomen of a y ki d, especially local flare (T lloch BMJ 2 318, 1943; Shaffer et al.: J 1.3 17 1943) Percutaneous absorption can cause a y toxic phenomenon that ral administration can (Pete kin: BMJ : 1 1945) Sensitization from sulfonamide medication is flared by contact with sulfonamide ren m h as nail lacquer may ontain. Treatment of sulfonamide intoxication: para-aminobenzoic cid, o hemically related procaine 1% 5 c.c., subcutaneously each 4 hours (Dixon: Pers. comm. 1945) If patch test is positive, oral testing is hazardous (Phillips: BJD 58 212, 1946) Cont ct sensitization is more likely to develop if kin is inflamed: ex perime t l sensitizat on b Gottschalk and Weiss (ADS 56 775 1947) Varieties of reactions (Erski e: BMJ 2: 104 1930; Dowling and Lepper: J 121: 1190 1943) Sensitization f om topical use (Shaffer et al. J 123 17 1943 Sulzberger et al. JAllergy 15:

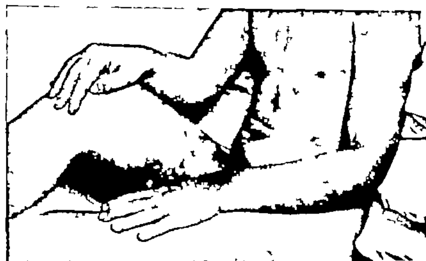


Fig. 182.—Sulfonamid eruption which ppeared on 9th day of administration f drug. Photograph on 10th day (Thompson BMJ 2: 13 1939)



Fig. 183.—Pemphigoid sulfonamide eruption (Bloom NYSJM 43 1499 1943)



Fig. 184.—Bullous sulfathiazole eruption seen on rm and forearm. (Dr J Lamar Calloway)

92, 1947) Fixed eruptions (Loveman and Simon: ADS 40: 99, 1939 McGuire and Shaffer: ADS 5.: 343, 1945; Leifer: ADS 53: 125 1940; Philpott: ADS 63: 776 1951) Photosensitization (Epstein: JID .: 43, 1939; Blum: JID 4 159 1941; Park and Platts: BMJ : 308 194.; Clark: J 123 968 1943; Watkinson and Hillis: BMJ *: 609, 1947; Sidi and Dobkevitch: abs YBD 1949 p. 1 ; related chemicals with amino group in para position on benzene ring) Initiation of psoriasis (Philpott: ADS 55: 825, 1947) Acquired epidermolysis bullosa, 3 cases (Bloom: NYSJM 53: 1077 1953) Fixed eruption of male genitalia, simulating secondary syphilid (Doyle BMJ *: 1530 1934)

Sulfur, Colloidal.—Urticaria, erythema, fever vomiting, diarrhea, cramps (QMN: J 110: 458 1938)

Tapazole.—See Methimazole

Terramycin.—Diarrhea, anal soreness (Willcox: Lancet : 154, 1951); see Moniliasis, etiology Scarlatiniform rash (Hay and McKenzie: Lancet 1: 045, 1954)

Testosterone.—See Androgen.

Tetanus Toxoid.—Urticaria (Cooke et al.: J 114: 1854 1940)

Tetracycline.—Diarrhea, pruritus ani; intolerance less frequent than from Aureomycin (q v) or T rramycin (q.v)

Thallium.—Alopecia, nephritis, formication in hands and feet, encephalitis, arthralgia, gastrointestinal pain, anorexia, insomnia, thirst, depression. Transverse bands of nails (Philadelphy: DWehn 93: 78 1934) Rat paste poisoning, treatment with sodium thiosulfate and vitamin B (Bromm: MünchMWehn 85: 1084 1938) Criminal Th poisoning (Steidle: MWelt 13: 1557 1939) Chemical detection in tissues (Gettler and Weiss: Am JChemPath 13: 322, 1943) No scientific basis for use of BAL in poisoning (Flesch and Goldstone: JID 15: 345, 1950) BAL cured rat poison case (Mazzei and Schaposnik: BMJ *: 791, 1949) See Tinea capitis, epilation with Thallium; also Prick et al. (abs J 141: 877 1949) Frank and Hirsch (J 150: 586, 1952); Lapiere and Demey Pousart (Annde D 79: 137 1952) BAL increased excretion fivefold.

Thiamin.—See Vitamins.

Thiocyanate.—Macular maculopapular dermatitis; itching and scaling exfoliative dermatitis (Watkinson and E anst BMJ 1: 595 194) Urticaria (Wald et al.: J 11 : 1120, 1939) Nondescript faint erythema resembling contact dermatitis (Green a d Snow: AIntM 64: 579 1939) Exfoliative dermatitis and necrosis of liver (Kessler and Hines: J 138: 549 1948)

Thiouracil and Thiourea.—Morbilliform eruption fever; erythematous macular, papular acneiform ra hes; pruritus; edema of legs (VanWinkle et l. J 130 343, 1946) Urticaria, neuritis, arthritis, mal ise (Williams: JClEndocr 6: 23, 1946) Thrombocytopenic purpura (Newcomb and Deane: La cet 1 179 1944); f tal agranulocytosis (Julian and H rris: J 139: 646, 1949) Alopecia (Clarke: J 147: 1711 1951)

Thorazine.—See Chlorpromazine Agra locytosis.

Tin.—Di-ethyl tin oxide with linoleic eid popular in France in 1953, poisoned several, killed some patients treat d fo furunculosis (Edit BMJ 602, 1954)

Tibione.—Agran locytosis (Da is et al.: SouthMJ 45 861 195)

Tragacanth.—Urticaria and atopy (Gelfand JAllergy 14 203 1943)

Tridione.—Purpura, aplastic a emia (H rrison et al. J 132: 11 1946)

Triethylene Melamine (TEM).—Maculopapular itchy rash spreading from arms to trunk and wrists (Fromin and Rubenstone: J 152: 915 1953) See Lymphosarcoma, treatment.

Trihexyphenidyl.—Numerous pulsating spider angiomas developed on face, neck and chest of 3 patients taking the drug for Parkinson's disease and disappeared when it was withdrawn (Holt: NEngJM 249: 318, 1953)

Tryparsamide.—See Arsphenamines.

Tuberculin.—Erythema, urticaria, erythema nodosum. Local reaction mild or severe, even sloughing Tuberculid.

Undecylenic Acid.—Morbilliform generalized rash (Reiches: ADS 62: 706 1950) Exfoliative dermatitis (Schiff: J 144 620 1950)

Vaccines and Bacterins.—Erythematous, papular and urticarial toxic rashes fever; erythema multiforme; herpes simplex exacerbations. See Antitoxins; Tet nus toxoid Frei ntigen; Tuberculin.

Vitamins.—See Hypervitaminoses A and D Lupus vulgaris vitamin D treatm t (Calciferol, etc.); Cod liver oil; Liver extracts. Vitamin A has caused erythema, exfoliative dermatitis, lopecia. Thiamin has caused angioneurotic edema (Eisenstadt MinnM .5 861 194.) macula itchy erythema disappearing after hyposensitization (Mitrani: JAllergy 15 150 1944) Nicotin c acid causes transient vasodilation, flushing itching, rticaria, dizziness, nausea, om ting (Sebrell and Butler: J 111: 2286, 1938) Vitamin B_{12} impu e, caused reactions (Young et al.: J 143 893, 1950); pure, gave tuberculin type reactions on ntradermal test in patient sensitive to Ni and Co (Rostenberg and Perkins: JAllergy 22: 466 1951) The B complex can cause urticaria, anaphylactic shock (Chitwood and Moore J 148 461 195 dangerous intravenously) Haliver oil with Viosterol caused fine papula rash resembling dry eczema (Pfister J 102: 633, 1934) Vitamin D intoxication exudative conjunctivitis, nausea, weakness, coma, peripheral and optic neuritis (M cree BJD 59 33, 1947) Wheat germ caused rash lik lichen planus (Newman CanadMAJ 43 175 1941) Rutin ca sed conjunctival petechiae (Wolffe and Daniels: J 134 602, 1947)

URTICARIA

Symptoms.—Urticaria (nettle rash or hives) is an inflammatory affection characterized by the eruption of whitish pinkish or reddish wheals caused by transudation of fluid from vessels into tissue spaces in allergic response to the local release of a histamine like substance The lesions are evanescent and give rise to burning itching and stinging sensations. Wheals vary greatly in size and considerably in shape They usually appear suddenly They are elevations, pinhead to fingernail sized at first but frequently they coalesce to form irregular patches. Rarely they become purpuric and are followed by temporary pigmentation Any or all parts of the body may be affected, but the sites of predilection are the lower trunk buttocks, and outer surfaces of the thighs. In ordinary cases the lesions persist for several hours and then disappear spontaneously leaving no trace Rubbing usually renders the lesions worse instead of better and may provoke a new outbreak in regions previously unaffected The mucous membranes notably those of the larynx, may also be involved.

Visceral lesions (see also Angioneurotic edema) have been demonstrated with the gastroscope by Chevallier (AnndeD 7 113 1936) Transitory myocardial changes shown by EKG have been reported by Foster and Laymon (J 148 203 1952)

Acute Urticaria is the most common clinical type an attack extending over a period of 3 or 4 days. During this time crops of new lesions are constantly appearing after older ones have subsided. The disease may then disappear permanently or it may recur

Chronic Urticaria may consist simply of repeated attacks of acute urticaria extending over a period of months or even years. Or the individual may have lesions continuously with or without exacerbations.

Serum Sickness presents urticaria as one of its major symptoms. Its phenomena are thought to be due to release of the H-substance from the union of serum protein antigens and antibodies. Histaminase (Best and McHenry JPhys 70 349 1930) has helped many patients (Foshay and Hagebusch J 112 2398 1939) and failed in others. The antihistaminic substances are effective in palliating the urticarial element but influence the arthralgia little Cortisone and ACTH usually help this.

Angioneurotic Edema is a form of urticaria characterized by large single or multiple circumscribed evanescent edematous swellings. The lesions differ from urticaria only in size The regions commonly involved are the lips the eyelids, and the lobes of the ears, although the extremities trunk larynx and genitals occasionally are involved The lesions are somewhat more persistent than those seen in urticaria. The disease is sometimes familial (Fineman AnnIntM 14 916 1940) Of 73 cases in which the cause was determined 38 resulted from drugs and of these 15 were due to aspirin and 9 to codeine preparations, reported Bruun (JAllergy 24 97 1953) Inhalants or contactants accounted for 11 and allergic etiology was presumed in 24 more In 35 cases of the total of 132 the cause was not determined In treatment Kafka (MRec 246 441 1937) recommended ephedrine sulfate gr ¾ by mouth and starch water baths. In edema of the glottis, he found effective the repeated administration of adrenalin at intervals of ½, 1 2, 4 and 8 hours It is in these cases that a tracheal catheter or as a last resort tracheotomy may be required Antihistamine drugs are effective

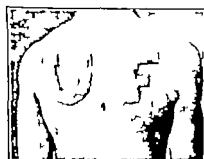
Urticaria From Heat and Cold— Physical allergy received brief consideration under Allergy (q v) Descriptions of heat sensitive cold sensitive light-sensitive and trauma-sensitive (dermographic) cases were collated by Duke (J 84 736 1925) there is an extensive literature to which reference is made in Edit (J 103 996 1934 see p. 1325) Reaction to the physical stimulus may remain local or become diffuse. A tourniquet proximal to cold induced whealing prevents the spread of wheals, which may become generalized when the tourniquet is loosened (Levine AIntM 56 498 1935)





Fig 165.—Urticaria, acute severe

Fig 166.—Urticaria with both ordinary and an [illegible] lesion



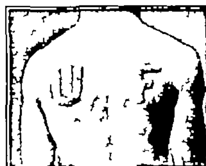


Fig. 167.—Dermographism urticaria elicited by mechanical irritation. Edema does not extend beyond the skin area directly irritated. (Dr W W Duke.)

Fig. 168.—Urticaria solaris, elicited by irritation by light. The area of edema does not extend beyond the area directly exposed to light. (Dr W W Duke.)

Reaction may involve tissues other than the skin, giving rise to coryza, asthma even abdominal pain, sometimes eczema. The application of cold in some individuals provoking redness, warmth and swelling locally is followed in a few minutes by a systemic histamine-like reaction of half an hour s duration with fall in blood pressure rapid pulse flushed face and faintness (Horton and Brown Am JMSc 178 191 1929) Collapse during swimming is a dangerous hazard in such persons (Horton et al J 107 1263 1936) Desensitization by graded exposures to cold has been accomplished.

Purpura associated with cold sensitivity was studied by Peters and Horton (PSMMC 16 631 1941) Familial cold urticaria has been reported by Urbach et al (ADS 43 366 1941) and Witherspoon et al. (ADS 58 52, 1948)

The release of acetylcholine by heat, physical exertion and emotion was the subject of interesting experiments by Grant et al (ClinSci 2 253 1936) Cholinogenic urticaria from heat and urticaria due to cold apparently are based on different mechanisms, concluded Hopkins et al. (ADS 38 679 1938) The classic abnormalities of response to choline esters given systemically and intradermally were observed by Morgan (JID 21 173 1953) who found



Fig 169 —Angioneurotic edema



Fig. 170.—Dermographism

somewhat reduced blood cholesterase in his 3 patients. When he experimentally exhausted the histamine content of a local region by using histamine-releasing compounds, the region no longer responded with urticaria.

Light Urticaria —See Urticaria solare (p 718)

Dermographism is characterized by the provokability of linear wheals by one s simply rubbing or stroking the skin with some pointed instrument Walzer (ADS 17 659 1928) demonstrated passive transfer of dermographia inducing factors in 7 of 12 persons tested. While Pyribenzamine will diminish the dermographic response it does not completely inhibit it (Baer JID 7 201 1946) Antihistamines can be used to inhibit the phenomenon more or less effectively so that for example a girl can attend a formal party without welts, but one does not know how to cure the condition. Dermographism is rarely seen in chronic urticaria and the two conditions should not be confused, noted Fisher and Schwartz (ADS 68 553 1953) In their 20 cases of dermographism without urticaria they were not able to find food or drug allergy

Black Dermographism is a physical phenomenon dependent on powder present on the skin When the skin is stroked with certain metals, particles scraped off leave their mark. The same reaction may be obtained on paper cloth and wood, reported Urbach and Pillsbury (J 121 485 1943) This has nothing to do with urticaria or dermographia See QMN (J 112 1749 1939)

PAPULAR URTICARIA (LICHEN URTICATUS)—The lesions are papular and yet possess some of the characteristics of wheals They are pinhead to pea sized, flat sharply defined and intensely itchy and are usually comparatively few in number This type is observed most frequently in poorly nourished children although adults are not immune The loins and buttocks are the sites of predilection. Diagnostically noted Laymon (J Lancet 52 29 1937) *papular urticaria shows wheals, only minor secondary changes, an even distribution* on the extremities and no constitutional symptoms, while in prurigo mitis there are lichenification, excoriation and scarring a heavy distribution on forearms and thighs and anemia and nervousness. Histologically the lesions of papular urticaria were of tuberculoid structure resembling positive skin reactions to insect bites reported Shaffer et al. (ADS 70 437 1954)

A Negro patient was cured with cod liver oil by Cole (ADS 33 657 1936) Patients generally improve in hospital even when their food is brought from home Pillsbury and Sternberg (AmJDisChild 53 1209 1937) reported good results in 85 per cent of their cases which were treated with calcium and parathyroid extract and similar results in 38% of those treated by calcium alone. Clinical improvement seemed chiefly concerned with the elevation of the level of the calcium content of the blood. They thought that evidence supporting a view of allergy as the cause of papular urticaria is meager Ellis (BMJ 2 118 1942) recommended potassium citrate, 10 grams t i.d. by mouth It is possible that the cause is external and that bedbugs or fleas may play a part Of 60 cases of Shaffer et al. (JID 11 293 1948) the majority were cured by using DDT locally and as a household spray and comparable experience was reported by Blank et al. (Ped 3 406 1950) Antihistamine agents failed to help cases studied by Cornbleet (ADS 60 1167 1949)

Etiology—The urticarial reaction consists essentially of three local changes in the skin, Lewis triple response a red area which within a few seconds becomes surrounded by a flare or flush, after which a wheal begins to appear (Ivy et al. ADS 58: 659 1948)

The triple response may be produced experimentally in man and some animals in response to mechanical injury heat cold and the intracutaneous introduction of many subst ces: allergens, histamine morphine, codeine, physostigmine, pilocarpine nd atropine. Wheaing is a specific response to these substances. The red spot at the site of introduction f the drug is pparently due to direct action on the blood vessels and occurs in denervated skin but the flare requires integrity of the axon ref x. The wheal, which will occur after n rve degeneration, is due to increased capillary permeability as proved by its discoloration by dyes give intravenously shortly before o d ri g the f rmation of the wheal. It does not occur if the dye is injected after the wheal has blanched. Protein in the wheal fluid approximates the concentration of protein in the blood plasma. A cuff which increases capillary pressure does not increase the size of wheals experimentally produced, but such wheals are of progressively smaller size as systolic pressure is approached, and wheating does not occur while blood flow is occluded. The wheal and flare are evidently due to the release of a substance by the cells of the skin when they are injured.

See Physiology Vascular Activity and Treatment, Antihistamine Agents. The different manifestations of urticaria, purpura, angioneurotic edema nd erythema nodosum merely represent differences in degree of allergic reaction and site of shock tissue, argued Lowe that (BJD 61 403, 1949)

Etiologic grouping of 170 cases of urticaria by Fink and Gay (BullJHH 55 280 1934) was as follows

1 Foci of infection 30% Of these 74% were cured by elimination of the focus.
2 Allergy to food, drug, ext rnal agent, scabies, 20%
3. Psychogenic, 18%
4. Endocrine, 6% All were females.
5. Unknown 25%

Hopkins and Kesten (ADS 29 358 1934) were able to demonstrate the etiologic factor in many cases, although some could not be ascribed to a known cause. They classified proved causative agents as follows

Acute Urticaria (single or repeated attacks)
A. Localized
1. Plant sect, jellyfish poisons

2. Nontoxic substances to which skin is sensitized
3. Heat, cold, light, mechanical irritation (many agents producing generalized urticaria may produce it locally)

B. Generalized
4. *Serum sickness, anaphylactic shock*
5. Food
6. Foreign substances absorbed through conjunctiva or respiratory tract
7. Drugs
8. Heat (exertion, excitement, fever)
9. Infections
10. Menstruation

Chronic Urticaria
11. Food (rarely)
12. Focal infection (frequently)
13. Animal parasites

An attack of urticaria occasionally follows the ingestion of a particular food or drug Allergy may be of obscure origin in some instances multiple factors being involved In some cases urticaria can be brought on by the specific action of physical agents such as light, heat cold, scratching and in heat sensitiveness by either mental or physical exertion Attacks may be precipitated by the ingestion or parenteral introduction of foreign proteins, especially serums and bacterial products.

Penicillin has been the commonest cause of urticaria in recent years in my experience and the high incidence attributable to it was noted too by Steinhardt (AnnAllergy 12 659 1954) although among his 500 cases were far more cases thought due to food allergy and psychologic factors than I should readily accredit.

Serum calcium estimations, studied by Greenbaum (ADS 16 553, 1927) in 63 patients representing all forms of urticaria, showed a normal or increased calcium level. He concluded that the administration of calcium salts to patients with urticaria generally lacks scientific basis. Increase of serum potassium during activity and diminution thereof during decline of urticaria, as is true also in asthma, was described by Rusk et al. (J 11 : *395 1939) Patients with urticaria who had low prothrombin levels were often relieved by vitamin K, 2 mg t.i.d. before meals (Black JAllergy 16: 83 1945) Cases associated with disease of the biliary tract and favorably influenced by cholagogues and biliary drainage were reported by Menagh (J 90 668 19**) The lack of vitamin C must be considered Chronic cases are usually due to foods, according to Kahn and Grothaus (SouthMJ 33 1086 1940) Women are more often affected than men. Inhalants, such as ragweed pollen, may cause urticaria as they cause asthma (Derbes and Engleshardt SouthMJ 37 7*9 1944) Perfume acted as an inhalant allergen in a case of Zakon and Kah (ADS 53: 11 1945)

Contact with some chemicals can ca se wheals in some perso s, a formald hyde (Rappaport and Hoffman: J 116 *656, 1941) and TNT (Preston and Watkins: ADS 53 134 1946) See Epstein (1955) on p. 146.

Of mal parasitoses inciting urticaria, scabies is the most l k l i testinal worms, *Schistosoma japonicum* and pediculosis of the scalp have etiologic potentialities. A patient who once had malaria, and whose chro ic rt caria wa puzzling, wa cured by At bri (Fineberg UCutRev 53: 100 1949) and this drug eliminated *Giardia lamblia*, diarrhea and urticaria, all of them, in a patient of Harris and Mitchell (ADS 59: 587 1949) Of 27 patients with amebiasis due to *E histolytica* 5 had urticaria and were cured with emetine by Giordano (abs YBD 1944, p. 175) Amebae accounted f r 19 of 33 chronic cases of obscure cause seen by Cohen and Criep (AmPractit 1: 246 1950) who cured many of them with carbarsone 0.25 Gm. t.i.d. for 10 days, although some equired emetine, 0.065 Gm. daily for 10 days. *Several patients when given ameb cides flared as with a Herxheimer* reaction.

Tinea of the feet can gi e rise to urticarial dermatophytids (Sulzberger and Kerr: JAllergy 2 11 1930)

Sweat, when injected intradermally into the skin of the subject from whom it was obtained, prod ced wheals observed Sulzberger t al. (JID 21: 293, 1933) The hypothesis was interestingly pursued that when sweat ducts are obstructed and sweat secretion occurs, intradermal dsorption of sweat ca produce discomfort, itching, wheals and aggravation of a coexistent dermatosis. See Anhidrosis.

Psychogenic factors causing urticaria were reviewed by Stokes et al. (ADS 31 470 1935) Emotional strain is more fatiguing than digging ditches. Urticaria when due to nervous exhaustion may respond to thyroid or ACTH. Frustration is *especially provocative (Saul and Bernstein* PsychosomM 3 349 1941) See Blitz (NYSJM 39 1309 1939) Kaywin

(PsychosomM 9: 131 1947) Attacks of urticaria in chronic cases were highly correlated with traumatic life situations, especially of resentment according to Graham and Wolf (J 143: 1396 1950)

Endocrine imbalance especially hypothyroidism, is by no means a rare cause of chronic urticaria Premenstrual exacerbations may respond to estrogenic substances, and endocrine balance should be established in any vexing case When endocrine medication is needed it is usually thyroid that helps the patient (Ravitch JCutDis 25 612 1907) If estrogenic substances are given to a patient with chronic urticaria and the patient becomes worse thyroid can be expected to prove helpful. The dose must of course be a correct one (see Acne treatment) Sensitization to the patient s own corpus luteum hormone was reported by Guy et al. (ADS 63 377 1951) and benefit was obtained by hyposensitizing injections of corpus luteum extract. See Geber (BJD 51 265 1939) Zondek and Bromberg (JAllergy 16 1 1945) Phillips (AnnIntM 30 2 364 1949)

Blood transfusion from a donor with urticaria resulted in a rash in the recipient whereas a later transfusion when the donor was not urticarial, did not (Tedstrom: JAllergy 5 303 1934)

Pathology —A wheal is a reversible acute inflammatory edematous lesion due to the action of a toxic agent which may reach the dermis from within or from without. Changes occur in papillary and subpapillary regions of the dermis and consist in vascular dilation with profuse outpouring of serum and white cells. The dilated vessels are filled with leukocytes. Throughout the area perivascular infiltration is prominent.

Diagnosis.—The wheal is a distinctive lesion A patient seen when wheals are absent shows perhaps macular erythema where lesions have faded and excoriations. The history of evanescent lesions, often called blisters by the patient is acceptable When urticaria has been identified, the diagnostic problem has commenced, not ended. A little scabies with much urticaria used to be a relatively common confusing picture.

Fluorescein given intravenously during an attack of urticaria is concentrated in the lesions, as demonstrated in ultraviolet light (Herrmann JID 7 210 1946) Concentration of bile pigment was noted in the urticarial lesions in a jaundiced patient by Derbes and Engelhardt (ADS 48 310 1943)

Prognosis.—An ordinary attack of acute urticaria is self limited and the lesions shortly disappear spontaneously or respond promptly to palliative antihistamine administration. Chronic urticaria usually proves to be a vexing tedious problem.

Treatment.—In acute cases occurring in persons who have not had hives before or have had attacks only a time or two one is not especially concerned with the cause which might be an unusual or contaminated food or a recently taken allergenic drug Palliation is generally simple using a light diet perhaps a saline laxative, tepid or cool baths with a cupful of baking soda to the tub of water phenolated calamine lotion, interdiction of any medicine not prescribed by the physician and an antihistamine drug of which my favorite is Chlor Trimeton, the dose for an adult being 4 mg every 4 to 6 hours, q s. to obtain relief. Capsules containing ephedrine 3/8 grain with Amytal 3/4 grain t.i.d. may be quite helpful. Excessive ingestion of caffeine is to be condemned, for patients who have not slept are likely to drink too much coffee which further interferes with the possibility of their obtaining rest See Forman (SouthMJ 44 11 1951) Subcutaneous injections of 0.5 cc 1 1000 epinephrine given as often as each 30 minutes may yield excellent relief Seldom indeed have I recommended intravenous injections of Benadryl though it can be so given (Goldman RockyMtMJ 44 1007 1947) or aminophylline (Turner JAllergy 20 307 1949) or procaine the dangers of which were pointed out by Waldbott (J 133 1301 1947)

Cerebral edema complicating skin allergy was relieved by intravenous hypertonic glucose by Murrell and Murrell (SouthMJ 43 950 1950) Laryngeal edema can force an emergency tracheotomy on the patient and the physician, who is obliged to respect urticaria as a dangerous disease

Chronic cases tax one's resourcefulness, sometimes considerably. While initial orders given to the patient are practically the same as in acute cases, the further steps in my practice include meticulous elimination of the possible etiologic influence of drugs (aspirin often enough), parasites (scabies, vesicular tinea, pediculosis, stool examinations), focal infections (teeth especially), endocrine imbalance (hypothyroidism especially), consequential anemia (iron and B_1 cure some cases), food allergy (not too common in fact, determined by elimination dieting), contactants and inhalants (soap, fabric finish, perfume, cosmetics occasionally) and psychologic stress.

The patient should receive a painstaking physical examination. The history must be adequate with respect to drugs (suspect vitamin pills, even contraceptive vaginal instillations, but penicillin is more likely), endocrine function, eating habits, the circumstances of exacerbations if urticaria comes occasionally rather than daily, and the possibility of emotional factors. Purposeful laboratory study must be undertaken. I like to have early in the case the red blood cell count, hemoglobin, serum total protein, blood sugar, urinalysis and stool examination. The white cell count and the proportion of eosinophilia are worth learning. More than once a gastric analysis showing no free HCl has provided the solution to the problem, in my experience. Since recognizing the importance of external parasites, drugs, foci of infection, endocrine factors and emotional influences, I have not failed, thanks to palliation with antihistamine drugs and sometimes cortisone, to manage successfully the large majority of my patients.

The detection of food allergens can be accomplished by the method of Winston and Sutton (Pract 160: 347, 1948). A single simple food, not a mixture of foods, is tested by eating it and waiting until the following meal to see if it has caused urticaria. Water, cane sugar, and noniodized salt are permitted freely, and rice, oatmeal, beef, beets, milk, and bread are tested at successive meals. A food that has been tested and is not followed by urticaria may thereafter be eaten right along. Thus, the number of foods which may be selected for the next meal rapidly increases. When urticaria follows the eating of a food, that food is tentatively considered to be an allergen and is not eaten again for one week. If urticaria follows a food upon retesting, it is considered proved to be an allergen. No new food is tested until the urticaria subsides. An antihistaminic of the tripelennamine hydrochloride type may be given to suppress the urticaria that may develop. The patient is given daily a list of the foods tolerated, those suspected upon initial testing, those proved causative upon retesting, and the new foods to be tested. This method, in contrast to skin testing, tests foods by eating them in the manner in which they are normally encountered. The specific ingested allergen is identified with precision, avoiding the uncertainty of the multiple choice elimination diets. The use of undiluted food extracts for skin testing and the elimination of all positively reacting food items was recommended by Kahn and Grothaus (SouthMJ 33: 1066, 1940). Food allergy is an unusual cause of urticaria, I believe. Manipulations of the menu were disappointing therapeutically to Sheldon et al. (JAllergy 25: 525, 1954).

Among various internal remedies Sutton Sr. found a cascara and bile salt preparation valuable. A pancreatic extract lacking insulin (Depancol, for example) may relieve at least while it is being given (Markel: ADS 39: 992, 1939). Calcium is commended by some but not by me. Epinephrine is best given in small doses frequently repeated until relief is obtained. Ephedrine often proves helpful. Wise (YBD 1936, p. 6) recommended pilocarpine in 1% aqueous solution, giving 3 drops first and increasing to 20 drops t.i.d., trying atropine later if this fails. The injection of a foreign protein, such as typhoid bacterin, sometimes proves beneficial (Traub: ADS 40: 368, 1939). Dilute hydrochloric acid, 30 drops t.i.d. with water, may help. Nicotinic acid was claimed to have cured some cases and to have caused others (Chambers and Bernton: JAllergy 15: 141, 1944). Vitamin K, 5 mg. q.i.d. the first day and t.i.d. on the second and third days, gave good results in three-quarters of 50

cases so treated by McInnes (SouthM&S 108 105 1946) Uritone (methenamine) 2 Gm intravenously once daily has been highly recommended (Littlejohn SouthM&S 101 463 1939) Cream of tartar (potassium bitartrate) half a teaspoon t.i.d. recommended by Grandma is not to be scorned

Cortisone acetate 25 mg t.i.d. or q.i.d., is especially helpful in cases of drug allergy and in those patients whose urticaria resembles serum sickness or erythema multiforme, and in patients suffering from emotional exhaustion ACTH sometimes works better than cortisone

Histaminase (Torantil) may be given in 5 unit enteric-coated pills, 2 or more tablets each 2 hours, sometimes with good effect on the hypothesis that urticaria is due to histamine and that the ingestion of the histaminase does away with it In 35 cases, Laymon (MinnM 25 466 1942) reported 21 cures with daily doses varying from 60 to 120 histamine-detoxifying units.

Chronic urticaria was attacked by Burgess (BMJ 1 662, 1939) by a program which included elimination of focal infection elimination of foods to which the patient is sensitive investigation of psychologic troubles, treatment of dyspepsia with hydrochloric acid, the administration of glucose and calcium and some method of desensitization such as autohemotherapy

Local applications which may alleviate the itching include carbolized calamine lotion with or without 1 to 3% of alcoholic solution of coal tar saturated aqueous solution of sodium carbonate or bicarbonate or of borax isotonic baths of sodium chloride ammonium chloride or magnesium sulfate and applications of vinegar Salves are not satisfactory Medicated soap woolen garments, and irritating local applications are among the things to be avoided. The relief of fatigue and irritability is usually important Interdiction of coffee and the administration of aspirin are serviceable measures. Some patients find no lasting relief despite every effort.

FOREIGN BODY GRANULOMAS

Responses of mesodermal tissues to substances gaining access to them in various ways are of basic interest in the comprehension of inflammation (q v) A number of cutaneous lesions depend on such phenomena.

Tissue Reactions to Lipids.—Mesodermal reactions to injections of olive oil cod liver oil and their fractions were investigated by Hass (APath 26 956 1938) Reaction to the whole oil was mild with olive oil, and some of it remained in situ unchanged after 3 weeks. With cod-liver oil however the reaction was inflammatory and none remained unaltered in situ after 3 weeks. The glycerol fractions provoked little reaction, but fractions of cod liver oil were more irritating than those of olive oil Nonsaponifiable fractions caused severe reaction, and sloughs resulted unless the dose was kept small destruction resulted mainly from the alcohol-soluble compounds of the nonsaponifiable fractions of both oils. Fatty acids provoked the most intense reactions of the lot and those from cod liver oil were more irritating than those from olive oil. Reactions to methyl esters of *saturated* acids were comparatively mild, for the material was rapidly hydrolyzed in the intercellular environment, acid crystals appeared in the zone and giant cells applied themselves to these foreign bodies. To methyl esters of *unsaturated* acids of cod liver oil the reactions were more intense and there formed in the intercellular regions quantities of semisolid, amorphous matter which served as a potent stimulus to the formation of giant cells. *Intensity of inflammatory response increased with increase in average unsaturation* of the lipoid fraction tested Epithelium partook of the reaction for cysts developed as a defense mechanism deriving demonstrably at times from the epidermis or from the accessory structures, so as to engulf the fibrotic zone of connective tissue reaction.

When unassimilable substances are injected, there occurs early an influx of polymorphonuclear leukocytes which subsides in a few days (Tompkins AmJSyph 20 22, 1936) Monocytes appear the third day after the injections they enlarge and become more active Clasmatocytes appear in 5 days, then epithelioid and transitional forms within 8 days. Giant cells of foreign body

and epithelioid types are present after about 10 days. When lecithin, which is assimilable is injected, focal increase in macrophages occurs but degenerative changes do not, and epithelioid and giant cells do not appear. Assimilable lipoids are removed from zones without residual modification of the tissues.

Reactions to fractions isolated from tubercle bacilli were described by Sabin (PhysRev 12 141 1932) see also Tuberculosis pathology. The phosphatid fraction is phagocytosed by monocytes, degrades them and provokes tubercle formation. The unsaponifiable waxes stimulate the production of undifferentiated connective tissue irritate and call forth leukocyte infiltration wax is the acid fast material. The acetone-soluble fraction, being a mixture of fatty acids, calls forth varied responses. Tuberculoprotein is provocative of plasma cell infiltration. The polysaccharides are chemotactic and toxic to neutrophile leukocytes and provoke necrosis and hemorrhage.

Tissue reactions of mice to killed tubercle bacilli appeared the same as to live bacilli and specific sensitization did not alter the histologic reaction, reported Pagel (AmRevTuberc 46 295 1942) although live bacilli induced eosinophilic granules in foam cells, while killed bacilli did not.

Intradermal injections of staphylococci in sensitized rabbits produced epidermal cysts and follicular comedones (Hopkins et al. JID 16 339 1951)

Petrolatum is capable of provoking acneic follicular dermatitis due to foreign body reaction (see Oil Acne)

Paraffinoma (Oleogranuloma) may follow injections of paraffin beneath the skin for cosmetic purposes. Such pseudoneoplasms develop in a fairly large percentage of the cases thus treated, but a considerable period of time from 6 months to 5 years, generally elapses before their appearance. The lesions are rounded or oval in outline and firm in consistency. In color they range from yellowish to reddish or purplish. Symptoms are practically absent but the deformity is sometimes extreme (Mook and Wander ADS 1 304, 1920 Gougerot BSocfrançD 41 1770 1934 Calnan BJD 65 565 1953) Similar lesions develop following the injection of paraffin mixtures employed as vehicles for mercurials, camphor and other medicines (Brown et al JLabClinM 29 259 1944 Conrad et al J 121 237 1943) Injection treatment of hernia may cause them (Whittaker PSMMC 11 22, 1936)

In paraffinoma the foreign substance is encapsulated in fibroconnective tissue. Cavernous spaces, surrounded by smaller cavities, give the area a Swiss cheese appearance. The mass comprises granulation tissue like that of early tuberculosis before caseation. Oil droplets are encased in giant cells.

Paraffin oil in the tissues shows vivid turquoise fluorescence under Wood's light (Cornbleet and Popper ADS 47 637, 1943) Tissue reactions to foreign lipids have been studied experimentally by Hass (APath 26 956 1938) Hirsch (AmJClinPath 9 279 1939) Tompkins (BullJHH 70 55 1942) The beeswax and peanut oil of penicillin injections may cause a pseudocellulitis presumably due to foreign body reaction (Lesnick et al. Surg 24 989 1948)

In diagnosis one must distinguish fibroma erythema induratum and keloid. The location color shape and history suffice for recognition.

The lesions progress to a certain point and then remain stationary. It was once thought that the tumors were harmless, but carcinoma and sarcoma have arisen in them. The only satisfactory treatment is total excision. X ray fails to benefit the condition.

Grease Gun Finger—An accident with a high pressure grease gun may force oil into the hand through a tiny puncture. Surprisingly painless at the time of the accident, swelling and numbness being the immediate symptoms, *pain follows and gangrene is likely*. The grease cannot be squeezed from the part even after incision (Byrne J 125 405 1944) See Smith (J 112 907 1939) Brooke (BMJ 2 1186 1939) Bell (BJPlasticSurg 5 138 1952)

Oil Blast Gangrene—Fine droplets of unassimilable oil may be forced into the skin under high pressure by a Diesel engine if a valve is opened during the operation of the machine and the body intercepts the blast of oil



Fig. 171.—Paraffinoma.



Fig. 172.—Paraffinoma, illustrating "Swiss cheese" structure.

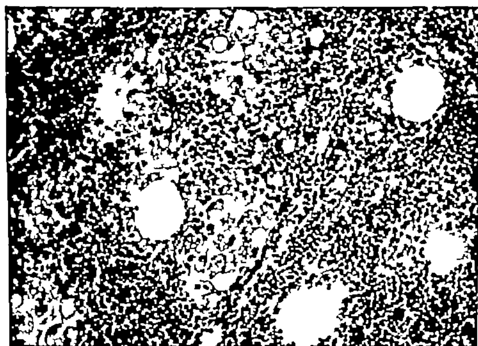


Fig. 173.—Phagocytosis of oil globules which have reached a lymph node from paraffinoma experimentally produced in a monkey (Dr Fred Weidman)

droplets. Swelling pain and likely gangrene result. Prompt free incision into the infiltrated tissue may prevent sloughing. See Dial (J 110 1747 1938) Hughes (J 116 2848 1941)

Air Blast may cause an injury analogous to the percutaneous injection of oil under high pressure though subcutaneous emphysema with typical 'crackling' swelling generally recedes spontaneously within a few hours (Whitewell BJIndustM 1 179 1944 Desmond BMJ 1 842, 1947)

Metallic Foreign Bodies may be carried into the skin by *showers of sparks* from spot welding (Reynard and Smith BMJ 1 843 1947)

Lipogranuloma (Fat Necrosis) is characteristically due to trauma with resultant necrosis of underlying adipose tissue and the formation of benign inflammatory tumors. The lesions are generally of hazelnut to walnut size, and somewhat raised above the skin level. They are purplish or reddish at first firm but becoming cystic. The breast is a common location and the *tumor must be distinguished from malignancy* (*Dunphy ASurg 38 1 1939* Livingston and Lederer SGO 68 230 1939) The scrotum was the site in 3 fat little boys noted by Hinman and Johnson (JUrol 41 726 1939) Trauma accidental or surgical is the most frequent causative factor but a history of trauma was present in only 41 of 110 breast cases reviewed by Adair and Munzer (AmJSurg 74 117 1947) Attachment to the skin existed in many of these and the resemblance clinically to cancer was notable in 45% positive diagnosis requires gross and microscopic examination of excised tissue.

The course of the lesion is chronic with the likelihood of rupture through the skin and the discharge of sterile oily and caseous material. Histologic study reveals foreign body reaction with numerous phagocytes and giant cells. Treatment should be expectant in early cases which may resorb. Excision, a speedy and satisfactory procedure often becomes necessary. If spontaneous healing takes place it is sluggish to do so, and the lesion may be called a *sclerosing lipogranuloma* (*Smetana and Bernhard SouthMJ 43 702, 1950*) See Edit (J 112 631 1939) Smetana and Bernhard (APath 50 296, 1950) Opeskin (SouthAfrMJ 25 778 1951)

Refrigeration may produce adiponecrosis of the face with circumscribed benign infiltration, which disappears spontaneously in a few weeks (Haxthausen BJD 53 83 1941) Such cases have occurred in military aviation

Fat Necrosis in the Newborn.—Fat necrosis such as occurs in adults may also occur in infants. *Gray (BJD 45 498 1933) distinguished (1) edema* neonatorum, which is true edema, perhaps from hunger and hypoproteinemia (2) scleroderma which is true scleroderma and very rare (3) induration secondary to fatal disease described as preagonic cadaveric induration of the celluloadipose tissue and (4) fat necrosis which is a benign induration. This disease is a self limited, localized process affecting areas which are usually symmetrically situated over the bony prominences. The patients, born after difficult labor as a rule, are usually well nourished and of large size differing from patients with sclerema (q v) which affects debilitated infants and generally proves fatal

The lesions become manifest in 2 to 20 days after birth as deep-seated, subcutaneous indurations. They range in size from small nodules to large areas covering the greater part of the back and buttocks, and appear to be slightly elevated above the niveau. The color is usually bluish red at the outset, suggesting at times a phlegmonous process. This disappears gradually the skin assuming its normal color even before the lesions have softened and disappeared. The surface of the skin is usually smooth. The lesions are not tender. The induration of the subcutaneous tissue dose not pit on firm pressure nor does it allow the skin to be pinched up in folds. The hardness resembles that of wood or rubber. The areas have fairly well-defined borders, and small nodular lesions are usually freely movable. Fluctuation has occasionally been noted. The favorite sites are first the back, then the cheeks,

arms, thighs, and buttocks. Almost every part of the body may be affected except the palms and soles, abdomen, inner aspect of the thighs, and axillae. An exceptional case with internal adipose tissue involvement was studied by Zeek and Madden (APath 41 166 1946) The course of the disease includes a period of evolution and one of involution both processes may be present simultaneously Softening and absorption of the indurated areas begin from the fifth to the sixth week and are complete as a rule in 3 or 4 months. The



Fig. 174.—Sclerema neonatorum, showing fat necrosis in deeper part of panniculus (Dr A. M. H. Gray)

Fig 175—Sclerema neonatorum, Sudan III stain, showing disintegration, liquid fat and cellular infiltration of fat globules. (Dr A. M H Gray)



Fig 176.—Sclerema neonatorum. Subcutaneous tissue shows clefts underneath of fatty acid crystals, giant cell response to altered fat and rosettes of crystals within some giant cells. (Patient of Dr Patricia Hart Drant photomicrograph from Dr Fred Weidman.)

lesions disappear completely and only in rare instances do they leave any trace such as slight atrophy The general health usually remains good, the temperature is not altered and there is a steady normal increase in weight.

Diagnostic criteria of this well-defined disease are solidity of fat during life typical histologic structure including calcification and anisotropy of the crystals in frozen sections of fat roentgen demonstration of calcification; excess of calcium, phosphorus and cholesterol in the fat and raised melting point of the fat (Harrison and Simpson quoted by Belisario AustralJD 2 94, 1953)

Pathologic changes comprise mainly necrosis of fat and epithelioid and giant cell reaction thereto. Protoplasmic meshes surround spaces formed by elongated needlelike crystals of neutral fat which is dissolved in preparation. In the fat cells there are similar crystals in rosettes or sheaths. Some giant cells are filled with crystals radiating from the center. There is evidence (McIntosh et al. AmJDis Child 55: 112, 1938) that infant and adult fats are chemically different: in the newborn the melting point is higher than normal body temperature because infantile fat is lower in olein content than adult. Obstetrical trauma is the main precipitating factor in infantile fat necrosis, and the triglycerides are altered mainly in their physical aggregation for in scleredematous tissues no lipase is present which is demonstrably capable of hydrolyzing them. Tozzati and Hansen (PSExpB 46: 325, 1941) reported that the abnormal fat is largely palmitic and in sclerema contains an excess of saturated fatty acids of low melting point and molecular weight.

See Fox (ADS 27: 237, 1933), Lichtenstein and Rader (SouthMJ 30: 527, 1937); Cornbleet and Rattner (ADS 40: 829, 1939); Reich (ADS 45: 342, 1942); Davis and Brain (JIJD 59: 312, 1947); Hughes and Hammond (JPed 32: 676, 1948); Nooljin et al. (JID 12: 331, 1949); Keiser (abs J 152: 1484, 1953) case attributed to DDT intoxication; Brain (JIJD 65: 373, 1953) case resolved in 3 months; Collins et al. (AnnSurg 138: 880, 1953) followed hypothermia used in surgery for congenital heart disease.

Indelible Pencil Injuries.—The basic aniline dyes used in making the leads of indelible pencils may provoke inflammatory necrotizing and foreign body reactions, the seriousness of which is partly dependent on their location. Ocular injuries have frequently been reported and in some cases the eye has been destroyed. The hands are especially liable to the injury. The point of the pencil is accidentally introduced within the tissues and perhaps broken off. The result depends on the chemical nature of the lead: toxicity increases among the aniline dyes from green, yellow, red and brown to blue, methyl blue being sufficiently poisonous to cause systemic reactions such as diarrhea and icterus. The acidic and neutral dyes cause little inflammation, but the basic ones do. Within an hour after the injury irritation is apparent, and within 24 hours there is evidence of necrosis, which is aseptic and lacking in leukocytes. The central semiliquid material is stained with the dye, and sloughing may follow or the necrotic matter may become walled off so as to form a pseudocyst, or perhaps it becomes merely a mass of colored granulation tissue. Since the dye dissolves slowly and diffuses slowly the lesions may persist for weeks or months, sometimes undergoing spontaneous acutely inflammatory exacerbations. Best treatment if it is anatomically applicable, is excision. To attempt to remove the fragile material with a forceps through a small hole results in crushing it and in the production of a violent exacerbation of the lesion. Mere incision and drainage are followed by recurrences of symptoms (Mason and Allen: AnnSurg 113: 131, 1941, hand cases; Srokolik: AmJOphth 10: 515, 1927, eye cases).

Silica and Silicates, notoriously damaging to pulmonary tissues, also cause cutaneous lesions. Talc is magnesium silicate. Ground into the axillary skin by the pressure of a brace it caused a suppurative tumor in the case of deSavitsch (MAnnDC 9: 169, 1940). Tissue reactions to subcutaneous injections of quartz were studied by Irwin and Gibson (CanadMAJ 39: 349, 1938). Talc on surgeons' gloves may provoke serious trouble (Lichtman et al. SGO 83: 531, 1946) and gray nodules of talc granuloma at edges of old scars were described by Flenberg (APath 24: 36, 1937). Talc granuloma of the eye following surgery for correction of muscle imbalance was observed by McCormick (AmJOphth 32: 1252, 1949).

Silica granuloma developed in the cheek of a patient of Epstein (AD 71: 24, 1955) several years after an accident resulting in the introduction into the skin of a splinter of glass. The histologic reaction was sarcoidal and cortisone had a promptly beneficial therapeutic effect. Edema and inflammation since they appear in such cases long after implantation of the foreign substance may be due to allergy, the initial stages of which seemed recognizable to Epstein et al. (AD 71: 645, 1955). Silica granuloma appeared in a young woman 11 years after she scraped her knees on gravel, reported Crossland (AD 71: 457, 1955) who found in the sarcoidal tissue reaction the doubly refractile crystals, demonstrable under polarized light, which suggest, but do not identify silica. Positive identification requires roentgen spectrography. Papular lesions of the face followed injury in an explosion in the case of Arzt (JID 24: 165, 1955).

Potassium bitartrate (Seelig: J 128: 113, 1943) or heated gelatin powder (Correll and Wise: Sci 105: 570, 1947) may be substituted for talc on surgical gloves. Talc is an irritant ingredient of a powder intended for treating dermatitis of the feet if the epidermis is broken, for silicates provoke mesodermal tissue reaction.

Asbestos spicules may provoke tiny warts on the fingers (Alden and Howell: ADS 49: 31., 1944). An injection used in treating hernia by sclerosis contained silica and caused 4 cases of granuloma reported by Kaplan (J 151: 1163, 1953). See also Traumatic dermatoses. Dermatitis Venenata, industrial, glass wool.



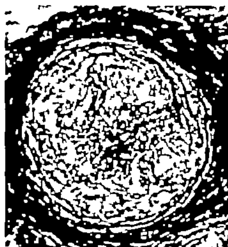




Fig. 177, 178, and 179.—Beryllium granuloma (Nichols and Dominguez: J 140: 855, 1949). Fig. 177 shows location of pathologic lesions deep in dermis. Fig. 178 shows an epithelioid cell nodule at high magnification. Fig. 179 shows the sarcoidal granulomatous process and its encapsulation.

Beryllium Granuloma.—Cutaneous exposure to beryllium can cause (1) contact dermatitis, (2) ulcers from implantation of crystals of beryllium sulfate, lesions which do not heal until the substance is removed, and (3) sarcoidal lesions in cases either of pulmonic berylliosis or of cutaneous in

jury with contaminated articles, such as broken fluorescent light tubes. Dusky purplish papules of from 1 to 3 mm diameter on the hands of a worker whose job it was to coat fluorescent light tubes with a liquid containing beryllium oxide and who also had disseminated pulmonary fibrosis, were noted by Pyre and Oatway (ArizM 4 21 1947) Similar lesions had been seen by Hardy and Tabershaw (JIndustHyg 28 197 1946) and the tuberculoid microscopic structure was described by Grier et al (JIndustHyg 30 228 1948) Lacerations with broken fluorescent bulbs may result in nodules and ulcerations closely simulating Boeck s sarcoid and the view that these lesions are due to beryllium and can be cured only by wide excision was stressed by Coakley et al (J 139 1147 1949) The structure of the pulmonary fibrosis and of the skin nodules is the same (Nichol and Dominguez J 140 855 1949)

Numerous cases have been recognized (Dutra ADS 60 1140 1949; Neave et al: ADS 61 401 1950; Gerrie et al: CanadMAJ 62: 544 1950 Lange et al: SouthMJ 44: 36 1951; Curtis: ADS 64: 470 1951 DeNardi et al: AIndustHyg 8: 1 1953) Since beryllium minerals are widely found, explosions may result in these granulomas, presumptive cases of which not recognized at the time they were reported include those of German (AmJClinPath 10: 45 1940) Sommerville and Milne (BJD 62 105, 1950) and Lohe (DWehn 1 1: 82, 1950)

The usual treatment is excision Cortisone ointment was accredited with a cure by Fisher (ADS 67 523 1953)

Beryllium granulomas of the skin were experimentally induced in hogs by Dutra (AIndustHyg 3: 81 1951) ACTH therapy yielded good improvement in a case of pulmonary fibrosis (Kennedy et al CanadMAJ 62 426 1950)

Lycopodium may cause foreign body granuloma The spores, introduced by means of the surgeon s gloves into surgical wounds, provoke inflammatory reaction and masses of tuberculoid tissue at the site of the operation. Persistent sinuses as well as masses of adhesions may be the result. Such sinuses must be distinguished from tuberculous and actinomycotic lesions (Antopol and Robbins J 109 1192, 1937)

Surgical Suture material causing granuloma has interested many authors (Orr ASurg 54 37 1947 Meade and Brewster AmJSurg 45 419 1939) The lesions are small sterile abscesses surrounded by dense fibrous tissue requiring sharp dissection for their removal

Plant Spicules as Foreign Bodies.—See trichrome dermatitis (p. 98)

Various Foreign Bodies have been reported as causing skin lesions hair impacted in the foot like a splinter (Schulze ADS 61 668 1950) finger and hand lesions from picking chickens, an industrial hazard (QMN: J 115 76 1940) a furuncular lesion where a sewing needle migrated (Ronchese Rhode IslMJ 32 264 1949 see Rogers Lancet 2 535 1942 on migration of foreign bodies) sulfonamide powder in a wound causing a chronic sinus tract and granulomas (Williams CanadMAJ 59 50 1948) tissue reaction to Gelfoam (Taylor and Kaplan ADS 62 548 1950) thorium dioxide injected into a breast causing a granulomatous tumor (Mora J 115 363 1940) See Hair Cyst.

DERMATOSES DUE TO VIRUSES

Viruses are organized living bodies which are usually invisible by ordinary microscopic methods of examination. They have a diameter of less than 0.[illegible] μ and can often be filtered through candles and membranes impermeable to ordinary bacteria. They have not as yet been cultivated in cell free media, but they multiply freely in the presence of susceptible cells in vitro or in vivo. They frequently invade one particular species of host, and tend to affect one particular tissue giving rise there to characteristic intracellular inclusion bodies, and they cause latent or overt infection followed as a rule by lasting immunity. The law of obligate communicability of virus infections was expounded, along with an able review of the nature of the agents, by Rivers (BullNYAM 14: 383, 1938). In the human being they produce diseases of as many varieties as bacteria do with comparable properties of communicability. Since viruses do not live free, but must exist intracellularly their ecology and epidemiology differ in important and characteristic ways from their bacterial analogues.

Viruses may be thought of as microorganisms, evolved by parasitic degeneration from larger organisms, manifesting reproductive activity, variation, survival, mutational and heritable faculties and interaction with their host (Burnet: Virus as Organism, Harvard U Press, 1945): "Every virus particle like any other organism derives by genetic descent from some similar particle." Elementary bodies of viruses are grouped within inclusion bodies, which are intracellular, in fowl pox, vaccinia, and molluscum contagiosum, while the virus of herpes simplex invades and spreads in axis cylinders of peripheral nerves. Many human pathogens can be cultivated and some cannot, in the chick embryo (Goodpasture: AnnIntM 13: 1, 1939).

A number of viruses, including that of herpes zoster for the first time, were cultivated on human skin grafted onto the chorioallantois of the chick embryo (Goodpasture and Anderson: AmJPath 20: 447, 1944; Blank et al.: PSExpB 69: 341, 1948).

See Sanders: APath 28: 541, 1939 (methods of cultivation); Ebert and Otsuka: ADS 48: 438, 1943 (review); Lennette: Sc 98: 415, 1943 (size, structure, chemistry); Rivers: Sci 95: 107, 1942 (immunology); Beveridge and Burnet (Cultivation of Viruses and Rickettsia in the Chick Embryo, HMSO, London, 1946); Schultz and others: J 136: 1075, ff., 1948 (Virus diagnostic laboratory); van Rooyen and Rhodes: Virus Diseases of Man, Nelson, 1948 (monograph); Bedson et al.: Virus and Rickettsial Diseases, Williams & Wilkins, 1950; Smith: Introduction to the Study of Viruses, Pitman, 1950 (fascinating reading 106 pp.); Markham: ADS 41: 261, 1940 (viruses not found in pityriasis rosea, psoriasis, lichen planus, lupus erythematosus, erythema multiforme, mycosis fungoides); Fisher: JID 8: 123, 1947 (chick embryo inoculations negative with warts, molluscum contagiosum, seborrheic keratoses, dermatitis herpetiformis, psoriasis, lichen planus, pityriasis rosea); Hillman: ADS 61: 210, 1950 (virus nature of pemphigus and dermatitis herpetiformis unproved); Rivers et al. (Viral and Rickettsial Infections in Man, Lippincott, 1952, p. 719); Rhodes and van Rooyen (Textbook of Virology, Williams & Wilkins, 1953, p. 441); Blank and Rake (Viral and Rickettsial Diseases of the Skin, Eye and Mucous Membranes of Man, Little, Brown & Co., 1955).

EXANTHEMATA

Under this title may be grouped the acute epidemic diseases with skin lesions which are important features of the diseases themselves and of especial clinical importance in their recognition. Several members of this group are of virus causation: smallpox, varicella, measles and German measles. Scarlet fever is streptococcic. See also Fourth, Fifth and Sixth Diseases, and Erythema symptomatic.

SMALLPOX

Symptoms.—The incubation period of variola varies from 8 to 12 days, and is usually about 10. The abrupt onset includes characteristically fever, intense frontal headache, severe lumbar backache and vomiting. The eruption is first visible on the third or fourth day. It begins as a macular erythema, on which develop shotty papules in a few hours. These soon vesiculate and they become pustular by the fifth day. There is *only one crop*, the lesions of which mature in the order of their appearance, earlier on the face and arms. The papules are usually discrete, but on the face confluence may occur, and the extent of the eruption on the face is a measure of severity. The vesicles are tough, deep-set, multilocular and umbilicated. The pustules show less definite umbilication, rest on hyperemic bases, and are smoothly rounded and of uniform size.

Usual Course.—Forehead and flexural surfaces of wrists are usually involved first. Face, forearms, palms and soles seldom escape. Mucosae are generally involved. The abdomen is usually least affected, and the eruption on the trunk is discrete. *The initial high fever falls with the appearance of*



Fig 180.—Smallpox, discrete eruption at its height. (Dr S. D. Sneltzer)



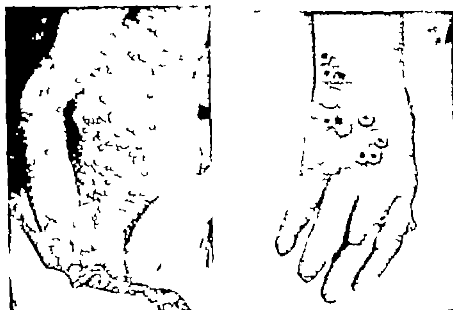


Fig. 181.—Smallpox (Dr Jay F Schamberg)
Fig. 182.—Smallpox on seventh day of eruption (Dr Jay F Schamberg)

the eruption concomitantly with abatement of the constitutional symptoms, but rises on the eighth or ninth day at the maturity of pustulation. On the ninth or tenth day of the eruption, many pustules rupture spontaneously or as a result of slight trauma. The lesions then begin to undergo desiccation, and

form dry brownish crusts. Shedding extends over a period of a month or more. Scarring which is depressed and atrophic depends on the depth of the lesions and the extent to which destruction of connective tissue occurs.

Secondary infection, as well as self inflicted trauma abet damage done by the disease.



Figs. 183 and 184.—Smallpox.



Fig. 185.—Smallpox, confluent on face. (Dr. Neilson Campbell.)

Sulfonamides may help (McCammon J 112 1936 1939) and penicillin has been reported to shorten the course of the disease (Jeans et al Lancet 2 44 1944 Weeks and McClelland USNMBull 47 707 1947)

The virus survives for several months at least in the dry crusts (Downie and Dumbell Lancet 1: 650 1947)

Varioloid is smallpox which has been modified by previous vaccination and partial immunity. It is generally milder in every way. The lesions are

fewer smaller and of briefer period of incubation, and there is less scarring Varioloid may be manifested by fever only (Napier and Insh Lancet 2 483 1942) On the other hand, immunity from vaccination may have fallen so low that more or less classic smallpox occurs (Conybeare Pract 157 191 1946)

Alastrim (Variola Minor) is milder than classic smallpox (variola major) but other diagnostic differences are not clear cut The inclusion bodies were thought to be larger and fewer than those in smallpox giant cells and ami totic figures were common and the reaction to Paul s test weaker in alastrim



Fig 186—Confluent smallpox with petechia in early stage (Drs. W tson Campbell and C S. N wman.)



Fig 187—Pemphigoid eruption in smallpox, a are phenomenon (D Sam E. Se hier)

according to Torres (ProcRoySocM 29 1325 1936) Cross immunity was not complete in experiments with monkeys (Horgan and Haseb JHyg 39 615 1939) The disease is less disfiguring than smallpox wrote Hay (SouthAfrMJ 12 639 1938)

Diagnosis of Smallpox.—In chicken pox prodromal symptoms are brief and comparatively mild The eruption comes early is polymorphous, appears in successive crops for 3 to 5 days, matures rapidly and involves first the cov ered surfaces rather than exposed areas. Its vesicles are monolocular They are superficial fragile and rarely umbilicated Each rests on a wide irregular erythematous flare Cases of dermatitis medicamentosa particularly from

iodide and bromide, do not as a rule have severe constitutional symptoms and the lesions do not involve the hands and wrists by predilection. History is important. In the pustular syphilid the papules are not hard or shotty. The varioliform syphilid prefers the perioral region especially in Negroes. There is no tendency to vesiculation. Constitutional symptoms are comparatively mild. There are general lymphadenitis, mucosal involvement and positive serum reaction. The usual diagnostic error made even by experts is to mistake smallpox for chicken pox (Smith BMJ 1 179 1948). One should distinguish hemorrhage into the pustules of smallpox from purpura variolosa which is rapidly fatal. See Dept Preventive Medicine Leeds Univ (The Diagnosis of Smallpox Lumby 1951)

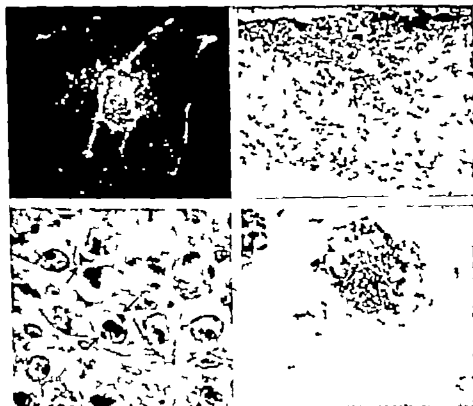


Fig. 188—Cultivation and demonstration of virus of smallpox (Buddingh AmJHyg 28: 130 1938)

Upper left Chorioallantois of chick embryo, actual size, showing gross alteration produced by inoculation with variola 72 hours previously. The unfixed, fresh specimen dark field photograph.

Upper right Chorioallantois, sectioned 72 hours after infection, showing inflammation of epithelium, proliferation, and vesicle formation.

Lower left Guarnieri bodies seen by high magnification of tissues shown at upper right.

Lower right Paschen bodies seen in and about the smear of an infected epithelial cell; 72 hour lesion prepared by the Morosow technic

The virus of smallpox causes a distinctive infection of the chick chorioallantois, which varicella does not (Buddingh AmJHyg 28 130 1938; Bohls and Irons: AmJPubH 32: 300 1942). Vaccinia and variola can be distinguished by chick embryo inoculation (North et al. MJAustral 1 437 1944)

A flocculation test utilizing a suspension of material from the lesions incubated with an antivaccinal rabbit serum, is both rapid and useful (Craigie and Tulloch Spec. Rpt. 156 M. Res. Council London, 1931)

A complement fixation test more sensitive than the flocculation test was described by Craigie and Wishart (CanadPubHJ 27 371 1936)

Scrapings from the bases of early lesions may be stained with Löffler's flagellar mordant and carbolfuchsin so as to demonstrate distinctive elementary bodies, larger than those of varicella (Van Rooyen and Illingworth BMJ : 526, 1944)



Fig. 189.—Accidental vaccination of hand.

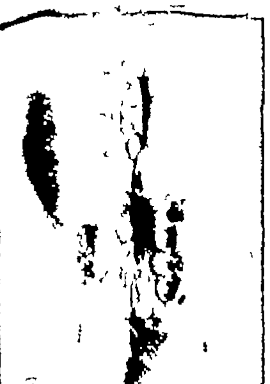


Fig. 190.—Vaccinia involving child's vulva. (Dr Hans H. [illegible].)

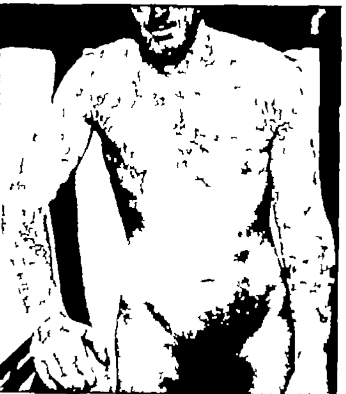


Fig. 191.—Generalized vaccinia, due to vaccinating a man who previously had eczematous dermatitis. (Dr Fred Weidman.)

Identification of the elementary bodies of variola and vaccinia, by microscopic means indistinguishable, can be made by electron micrography (Nagler and Rake: JBact 55: 45, 1948). Electron micrographs of the development l forms of vaccinia virus were published by Gaylord and Melnick (Sci 117: 10 1953).

PAUL'S TEST.—The content of the vesicopustules, scraped with a sterile knife onto a glass slide and dried for 3 days, is taken up with 50% glycerol in water and inoculated into the scarified cornea of a rabbit. Minute elevations of the corneal epithelium appear within 36 hours if the test is positive. Paschen bodies are found in these elevations. See Michelson and Ikeda (ADS 15 139, 1927); Paul (WienKlinWchn 60: 862, 1910); Guarnieri (AItalBiol 19: 193 1893), Paschen (ZtschrBakt 1 4: 89 1932) Amies (Lancet 2: 658, 1932) elementary bodies; Ebert and Otsuka (ADS 48 635, 1943).

Vaccination.—One applies a droplet of vaccine on the clean skin, which must be free of antiseptic (acetone may be used) the needle is pressed tangentially to the skin several times in such a manner that the point breaks the horny layer in an area some 3 mm. across and the lymph is allowed to dry. No dressing is necessary (Leake BHRpts 42 221 1927). The sole may be used for inoculation for cosmetic reasons, in infants (Cantor BMJ 2 1050 1953). Intracutaneous vaccination is feasible, using cultured vaccine virus (Rivers and Ward JExpM 62 549 1935). Vaccination of the newborn is satisfactory and safe (Donnally and Nicholson J 103 1269 1934). Vaccination during pregnancy is said to be safe (Bellows et al. PHRpts 64 319 1949) yet a fetus was born with generalized vaccinia 28 days after vaccination of the mother (Lynch ADS 26 997, 1932). See Crookshank (History and Pathology of Vaccination London 1889) and Downie (BMJ 2 251 1951) history.

COURSE OF NORMAL VACCINATION.—On the first day there is a traumatic wheal. Nothing is visible for a day or so then a tiny group of coalescing vesicles appears on a small zone of erythema. From the fifth to the ninth day the vesicle grows, and the area of redness extends. There is fever of 101° F to 102° F on the eighth and ninth days, with some malaise. The vesicle fluid is clear at first but becomes cloudy and eventually purulent. From the ninth to the twelfth day the zone of erythema spreads widely with thickening and induration of the surrounding skin after the twelfth day involution occurs with blackening shrinking and loosening of the crust at the periphery. The crust eventually drops off leaving a red and pitted scar which slowly pales and becomes atrophic (the Jenner reaction Gloyne J 122 395 1943). See Armstrong (PHRpts 44 1871, 1929).

INTRACUTANEOUS VACCINATION offers less opportunity for secondary infection and by its use one may secure a take in individuals who repeatedly fail to react to ordinary methods. It may result in generalized vaccinia or a nodular subcutaneous scar (Jacobs and Orris JPed 17 626 1940).

REVACCINATION.—An individual who has been vaccinated will respond to subsequent vaccinations sometimes in the same degree as to the first. Usually however the lesion appears sooner and involutes more rapidly. Revaccination is simple harmless, and dependably protective. It should be performed whenever real or suspected exposure to smallpox has been incurred. Heat killed inactivated vaccine induces responses simulating reactions of immunity this immediate reaction is a manifestation only of allergic sensitivity to the vaccinia virus and should not be mistaken for proof of immunity nor called the reaction of immunity according to Benenson (J 143 1238 1950).

VACCINIA is a highly infectious disease dangerous to unvaccinated individuals who already have dermatitis, and readily transmissible (Traub ADS 60 1021, 1949) causing even epidemics of cowpox (Hamburger abs J 138 782, 1948). Because of exposure to smallpox, patients of a dermatological ward, other than those with atopic dermatitis, were vaccinated by Dewar and Finn (GlasgowMJ 35 141 1954) only 4 complications occurred in 84 patients.

Generalized vaccinia is rare. It is likely however to complicate the ill advised vaccination of a person already suffering from some widespread dermatitis. Vaccinia complicating infantile eczema results in a typical syndrome resembling Kaposi's varicelliform eruption (Ellis: J 104: 1891 1935). Death

may result (Petersilge and Toomey APed 61 454 1944 Keidan et al. ADisChild 28 110 1953) Clinical differentiation from Kaposi's eruption is possible (Riley and Callaway JID 9 321 1947)

COMPLICATIONS include regional or generalized (multiple) vaccinal lesions, urticaria, purpura, erythema multiforme and secondary infection such as infectious eczematoid dermatitis (Bloch Lancet 2 504, 1942) rarely keloid (Skeer ADS 42 1165 1940) See Curth et al (JID 10 197 11 167 1948) Accidental vaccinia of the eyes can generally be avoided (Laval AOphth 24 367 1940) Vaccinia of the eyelid was apparently benefited by Aureomycin reported King and Forrest (J 153 31, 1953)

Bullous, pemphigoid complications were reported by Howe (JCutDis 21 254 1903) and by Mook (JCutDis 33 667 1915) and many of these such as have not been seen recently led to death The vesicobullous lesions seen by Mali et al (abs J 158 608 1955) involved the face, extensor aspects of the extremities, and upper trunk and disappeared in a week or two without scarring



Figs 193 and 194.—Vaccinia virus, above ×57 066, and below ×62,506 (Dawson and McFarlane, National Institut for Medical Research Nature 161 464, 1948)

Peripheral neuritis and radiculitis occasionally complicate vaccinia (Winkelman ANeurPsych 62 421 1949) Postvaccinal encephalitis, while rare killed 30% of 240 cases collected in Austrian experience 1925 to 1935 (Kaiser and Zappert Postvaccinal Encephalitis, Springer 1938) 27 cases were studied by Miller (ANeurol 69 695 1953) 16 of which were of encephalitis and 3 of transverse myelitis.

Paravaccinia (Red Vaccinia)—The lesion appears at the site of antismallpox vaccination as a red, rounded or cruciform papule with precipitous margins. The pea-sized papule reaches its peak of development in 10 to 14 days and regresses gradually passing through the color changes of a hemorrhage

MILKERS NODES AND SHEEP POX

Milkers Nodes.—Nodular inflammatory lesions infectious and transmissible from cow to man, and from man to man have been observed on the hands of milkers and others whose occupations bring them in contact with the usual source of the disease It may give rise to epizootics in stock, especially

in the summertime. Transmission to man may give rise to small epidemics. It produces characteristically granulomatous efflorescences at the sites of inoculation on the hands with or without lymphangiitis and secondary ex-



Fig. 194.—Orf. The lesion, contracted from a sheep, involves the eyelid. (Peterkin: BJD 49: 492, 1937.)

Fig. 195.—Milkers' nodule of finger: a Missouri case.



Figs. 196 and 197.—Milkers' nodules: lesions of fingers of one patient and thumb of another. Severe lymphocytic inflammation and subepidermal vesiculation of minor degree are seen in the photomicrograph. (Donnerve: BJD 49: 164, 1937.)

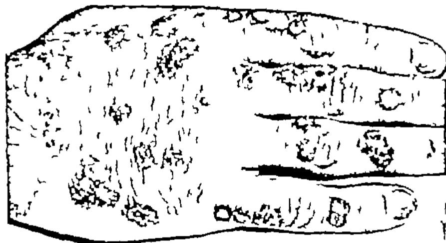


Fig. 198.—Orf. (Ferguson: BJD 63: 268, 1951.)

anthemas. The disease disappears without treatment in a few weeks, leaving no trace. Histologic study reveals an infiltration of lymphocytes and fibroblasts, with some polymorphonuclear leukocytes. There are no giant cells or

plasma cells. *The acanthotic epithelium shows some minute vesicles.* There are no inclusion bodies such as Guarnieri s. Paul s test is negative and patients take vaccinia in an ordinary fashion when inoculated (Becker J 115 2140 1940) The presumably causative virus has not been isolated (Nomland and McKee ADS 65 663 1952) but the disease was transmitted experimentally from man to man by rubbing biopsied material onto abrasions, by Sonck and Penttinen (ActaD-V 34 420 1954)

See Bonnevie (BJD 49 164 1937) Blank (ActaD-V 29 100 1949) Da is nd J nes (Lancet 2 1534, 1938), cowpox on hands f farmworkers; Findlay and Haig (BJD 64 451 1952) first report of South African cases, culti ation of infectious agent on chick chorioal lantois pathogenic *for cow not man*; Cawley *et al.* (SouthMJ 46 : 21 1953) *cases from* Vi ginia; Green (J 153 757 1953) calls attention to article in NOrlM&SJ 97 12, 1944 Sonck (ActaAllergol 4 241 1951) cases with secondary papulovesicular rashes on hands and forearms.

Orf (Sheep Pox, Ecthyma Contagiosum)—This contagious, pustular dermatitis of sheep known as orf to the farmers of Scotland is transmissible to man In the human Peterkin (BJD 49 492, 1937) described the initial lesion as a dark red papule which grows to the diameter of a threepence or half-crown. It is firm and practically painless. It resembles a huge molluscum contagiosum tumor with well marked central umbilication. The depressed center is covered with thin white skin and contains clear exudate The exudate gradually becomes purulent probably because of secondary infection, and granulations soon heap up If the lesions are treated with antiseptics, they tend to shrivel up in a few weeks without purulent discharge or granulations appearing See Schoch (ADS 39 1040 1939) Nomland (ADS 42 878 1940) Kingery and Dahl (ADS 51 359 194) Wallace (BJD 59 379 1947) Wheeler et al. (AD 71 481 1955) believed ecthyma contagiosum and sheep pox due to distinct viruses.

Scabby mouth of sheep a vesiculopapular eruption usually confined to the lips and surrounding tissue, has long been known in Queensland, Australia. This *can be transmitted to man* (Barrack AustralJD 1 135 1951) The infection in a man was successfully inoculated into a sheep and smears from the vesicles in the animal showed a virus (Lloyd et al. Lancet 1 720 1951) Isolation of the virus of orf and demonstration of its identity with that of contagious pustular dermatitis of sheep were claimed along with experimental transmission of the infection to man, by Blakemore et al. (BJD 60 404 1948)

Diagnosis.—The diseases of this group closely resemble one another Peterkin distinguished orf from milkers nodes by the fact that the lesion of orf in man is usually single and much larger than the lesion of milkers nodes, *is notably umbilicated does not cause lymphangitis such as often is seen in* milkers nodes, and in healing always passes through a stage of resemblance to granuloma pyogenicum Foreign body lesions due to hairs embedded in the skin of a milker s fingers are differentiated, such lesions being called milker s panaritium (Preser ZentralblChir 35 28 1908) Symmetrical calluses on the thumbs from milking by the Swiss method are plainly distinct from milkers nodes.

CHICKEN POX

Symptoms.—The period of incubation of varicella ranges from 11 to 24 *days, averaging about 17 Droplet infection is the method of spread,* and the disease is readily communicable Infectiousness is slight after the sixth day of the rash (Gordon and Meader J 93 2013 1929) The stage of invasion may be marked by some pyrexia, headache and malaise, but these symptoms are often altogether lacking Lesions usually appear in crops. Trunk, face and scalp are the sites of predilection. Volar lesions are only occasionally present. The eruption is at first macular and erythematous, and vesicles and vesicopapules develop in the centers of these areas within a few hours. The vesicular lesions are pinhead to pea-sized rounded, dome-shaped, monolocular and translucent with or without pinkish red hyperemic areolae. *The typical efflorescence of chicken pox resembles* a dew drop on a rose



Fig. 199.—Chicken pox. (Dr. J. F. Schamberg.)



Fig. 200.—Chicken pox. (Dr. E. Wood Ruggles.)



Fig. 201.—Chicken pox.

petal (Donnie) The vesicles rupture easily If not broken by scratching they generally begin to desiccate at the end of 48 hours. There is some itching The crusts are thin and of the same outline as the lesions. They become detached within a week to 10 days. The resultant scars are circular and atrophic. Hemorrhagic extreme cases are occasionally seen (Tilley and Warren BMJ 1 1265 1938) In adults the disease is likely to be severe.

Corneal involvement is probably not rare and it apparently is not dangerous (Loewenstein: BJOphth 24: 391, 1940) It begins deep in the cornea and rises to the surface but does not induce photophobia. Mucosal and visceral lesions have been described (Johnson: APath 30: 292, 1940) Intrauterine infection has occurred (Oppenheimer: BullJHH 74: 240 1944) Complications with pneumonia, otitis media, abscesses, suppuration cellulitis, erysipelas, septicemia, nephrosis and encephalitis have been observed (Bullowa and Wishik AmJDisChild 49: 923, 1935) Of 119 cases of encephalitis collected by Underwood (BJChildDis 32: 83, 177 241, 1935) 1 % died and 15% had lasting sequelae See Walcott (NEngJM 1 : 123, 1937); Waring et al. (AIntM 29 334 1942); Appelbaum et al. (AmJMed 15: 223, 1953); Humphries (JMAAla 23 198 1954) The severe virus type of pneumonia, with bilateral nodular infiltrations in the lungs, may be due to the varicella virus, for it clears as the skin lesions improve (Saslaw et al: AIntM 91: 35 1953)

The presumably causative virus was cultivated by Weller (PSExpe Biol 83 340 1953)



Fig. 202.—Chicken pox vesicle, showing location of fluid in the epidermis, which is free from inflammatory cellular infiltration Endothelial destruction has allowed perivascular hemorrhage Intense inflammation surrounds this vessel. (Johnson APath 30 292, 1940.)

Diagnosis.—See Smallpox. The Paul test is negative in varicella An eruption indistinguishable from varicella occurs in a small proportion of cases of zoster (q v) especially in severe ones (Bullowa AmJDisChild 49 923 927 1935) The relationship between the viruses of varicella and herpes zoster appears to be a close one but is debated. Postzoster serum may protect a varicella contact from developing the disease (Whigham and Handelman BMJ 1 812, 1944) Cross agglutination of the elementary bodies of herpes zoster and varicella was shown by Amies (Lancet 1 1015 1933) The elementary bodies prepared in pure suspension by high speed centrifugation are infectious, while the supernatant fluid is not (Eagles and Ledingham Lancet 1 823 1932)

MEASLES

Rubeola is an acute febrile virus infection characterized by catarrhal involvement of the upper respiratory tract and a diffuse, erythematous, macular eruption which ends with fading and desquamation. The incubation period

is fairly uniformly 8 to 10 days, but the appearance of the rash may rarely be delayed even until the twelfth day (Goodall BMJ 1 336 1936) The onset of the disease is gradual and the early symptoms include slight fever head ache chilliness, coryza lachrymation, sneezing cough, and photophobia Lesions may be noted first on the buccal mucosa as small, irregular bright red Koplik s spots, each of which is marked centrally by a minute bluish white speck. Koplik spots were observed in the mucosa of the colon of a man with a colostomy; such lesions doubtless account for diarrhea and gastroenteritis (Hobson Lancet 2 134 1940)

The eruption, which consists of small pinkish, slightly edematous maculopapules, appears first on the face and neck and then spreads rapidly to the trunk and extremities. On the abdomen and back the lesions often tend to form crescentic or arcuate patches surrounded by normal skin. The eruption is of a deeper darker red than that occurring in scarlet fever The peculiar shotty lesions of variola are never present. The fever and the catarrh persist until the eruption begins to regress. In severe cases, hemorrhagic measles may develop with petechiae or even extravasations of blood into the lesions. After the eruption has persisted for 4 or 5 days, it gradually disappears to be slowly followed by furfuraceous, branny desquamation

A presumably specific viru wa cultivated and propagated in tissue cultures by Enders and Peebles (PSExperBiol 66: 77 1954)

Diagnosis may be made in the prodromal stage by the demonstration of peculiar large multinucleated giant cells by Papanicolaou staini g of glairy mucu from high i the nose according to Tompkin and Macaulay (J 15 : 11, 1955)

The cough and malaise are ameliorated by Empirin with codei e. Cutaneous distress is palliated with cool compresses of aluminum acetate, 1:500 and inunctions of mineral o l. It hing responds to antihistamine drugs with some satisfaction Gamma globulin given at the time of exposure can prevent infection with passive immunity or markedly attenuate the severity of the disease if it is contracted. It benefits toxic patients. It may delay the appearance of the rash until after the f brile period.

Cases with bullous eruptions have been reported (Ronaldson: BJChildDis 34: 99 1937) If convalescent serum is i jected intradermally at the onset of the disease, the rash is inhibited at that site in the majority of cases (Debré phenomenon: Phillips: AmJDisChild 55: 1257 1938)

Measles is likely to interrupt pregnancy and has been found present in the newborn when the mother contracted the disease near term (Dyer: SouthMJ 33 601, 1940) The hazard to the mother is not great. Possible damage of the fetus resulting in congenital malformations (compare R bella) was reported by Hagström er (abs J 139: 1040 1949) When measles was introduced into the Faroe I lands, where there had not been a case in 65 years, 6000 of the 8000 inhabitant were infected (Panum: see Edit InternatMDig 53 164, 1948)

GERMAN MEASLES

The period of incubation of rubella lies probably between 14 and 21 days. The onset is fairly abrupt and is characterized by mild constitutional symptoms and usually the enlargement of postauricular suboccipital, and post cervical lymph nodes. The eruption consists of rounded or oval pinhead to split pea size, pinkish macules or maculopapules. It usually appears first on the face but quickly spreads to the chest, trunk, and limbs. The lesions are discrete as a rule but they may be grouped or even confluent. The rash seldom persists longer than 3 or 4 days, and its appearance is not followed by desquamation. Catarrhal symptoms, if present, are relatively mild. The patient s temperature seldom exceeds 100° F and there may be no fever whatever Relapses are infrequent.

Experimental inoculations have succeeded when nasopharyngeal washings or blood obtained 2 days prior to the appearance of the rash was used as the source of the virus by Krugman et al. (J 151: 285 1953) The incubation period proved to range from 9 to 16 days. Experimental rubella was contagious, and t caused both typical disease and rubella w thout rash. A virus grown and propagated in monkey kidney tissue produced the disease in volu teers, reported Anderson (La cet 1107 1954)

Complications include pneumonia, empyema, lymph node abscesses rthritis (Shaw: JIndianaSMA 29 227 1936) and meningoencephalitis (Briggs JPed 7: 609 1935) Purpuric lesions and severe adenitis were seen by Briggs among the later cases in the St. Paul epidemic of 1935. In a British epidemic of 1940 many patients had stiff neck, oc-

cipital headache and swelling of the oral and nasopharyngeal mucosa (Bennett and Copeman BMJ 1: 9*4 1940) While the throat might manifest follicular pustules, oral symptoms were not severe, though aching of the gums for 48 hours, starting usually on the second day was a complaint. Desquamation started as soon as the rash began to fade and in some cases was as intense as that of scarlet fever. Severe but transitory encephalomyelitis was attributed to rubella in a man studied by Mitchell and Pampiglione (Lancet 1-50 1954)

Fetal Injury—While practically without complications to the patient rubella in pregnancy is highly hazardous to the fetus, especially during the first 8 weeks resulting in cataract cardiac abnormality mental retardation, deaf mutism and other anomalies (Albaugh J 129 719 1945) The first recognition of congenital defect associated with maternal rubella was by Gregg (TrOphthSocAustralia 3 35 1941) See review by Miller et al. (ADS 62 477 1950) of anomalies associated with various dermatoses in the mother also Tedeschi et al. (NEngJM 249 439 1953) Cataract and microphthalmos as well as cardiac defects in 5 cases where the mother had rubella during the first 2 months of pregnancy were observed by Long and Danielson (Arch Ophth 34 24 1945) Such congenital cataract may be operated upon at an age of 2 or 3 months, before nystagmus begins (Goar and Potts AmJOphth 29 566 1946) Congenital deafness was of especial concern to Hopkins (AmJDisChild 72 377 1946) who reported 10 cases. Congenital heart disease interested Gibson and Lewis (AmJDisChild 83 317 1952)



Fig 101—Morbilliform rash of German measles (Dr J F Schamberg)

It is highly desirable that women have rubella prior to pregnancy and Anderson (MJAustralia 2 389 1950) was able successfully to inoculate volunteers with throat washings preserved virulent by refrigeration.

Diagnosis.—German measles differs from scarlatina in these respects its longer *period of incubation absence of severe systemic symptoms, particularly* fever and angina first appearance of lesions on face and forehead and absence of desquamation. The pinkish, evanescent character of the lesions, relatively mild nature or absence of respiratory symptoms and the presence of cervical lymph node enlargement will usually serve to distinguish it from measles.

HERPES SIMPLEX

Herpes Simplex is a specific virus infection, commonly manifested as fever blisters, which comprise an acute eruption of a group of vesicles set on an erythematous, swollen base. Early manifestations are sensations of itching and tension, followed by localized hyperemia. The patches are usually few in number and closely grouped. Vesicles, which range from pin point to large pinhead size and which are filled with clear fluid develop on the swollen reddened areas within a few hours. Suppuration may occur. If unmolested, the vesicles dry up and form thin, yellowish or brownish crusts

which drop off within 7 to 14 days. As a rule no scar results, but atrophic scars may follow severe cases. When the face is affected the lips, perioral regions and cheeks are the parts most frequently involved although the external ear particularly the auricle, is occasionally attacked The inner surfaces of the lips are sometimes affected Herpes of the genitalia is frequent Here abrasion is probable, and, when the patient is seen only a group of raw circumscribed erosions, the bases of the former lesions are visible





Fig. 204.—Herpes simplex, with herpetic fever and painful lymphadenitis.

Fig. 205.—Herpes simplex. This patient's husband had a similar lesion, at the same time on the left side of his chin.



Fig. 206.—Herpes simplex of penis.

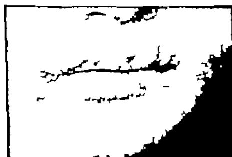


Fig. 207.—Herpetic stomatitis

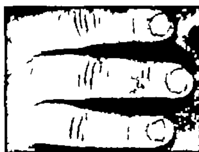


Fig. 208.—Recurrent herpes in unusual location.

The eruption can appear on any part of the body Finger and forearm lesions, with fever lymphangitis and lymphadenitis, were shown to be due to the herpes virus by Trice and Shafer (ADS 67 37 1953) Volar herpes was noted by Kipling and Downie (BMJ 1 247 1948)

Rarely does herpes produce lesions on the hard palate but it may by affecting the great superficial petrosal nerve inducing a kind of Hunt s syndrome (q v) because of the branches to the tympanic plexus and otic ganglion (Wakeley and Mulvany Lancet 1 746 1939)

Herpes simplex may be primary or secondary As a primary affection, its severity is occasionally considerable, with malaise fever and satellite lymphadenitis. The constitutional symptoms of herpetic fever' may precede the eruption some 24 hours or more The patient is generally a child, and stomatitis is the usual manifestation (Anderson and Hamilton MJAustral 1 308 1949) or vulvovaginitis (Scott NEngJM 250 183 1954) No specific treatment is as yet known (Edit BMJ 2 403 1954) although cortisone effectively palliative in herpes zoster deserves trial

Secondary herpes occurs in the course of many febrile diseases, including the common cold, influenza pneumonia malaria, meningitis, and salmonella food poisoning It frequently follows sunburn or fever therapy and may be quite severe Corneal involvement provokes acute disease with pain, lacrimation and photophobia the epithelial lesion being characterized by swelling vacuolization and necrosis, multiple dendritic or latticelike (Noé IowaSMSJ 29 400 1939) Cranial nerve palsies following general anesthetics were accompanied, for the most part by labial herpes and were attributed to herpes by Humphrey and McClelland (BMJ 1 315 1944) Herpetic encephalitis, with disorientation, drowsiness, scanty physical signs but severe histologic changes of malacia, has been recognized the 2 cases of Whitman et al. (J 131 1408 1946) were fatal and records of 10 fatal cases were gathered by Cambier (PresseM 63 286, 1955)

Herpes infection may complicate infantile eczema (Barrow BMJ 1 482, 1954) see Kaposi s Varicelliform Eruption.

After artificial pyrexia, symptomatic labial herpes was of higher incidence and greater severity in perso s who had previously experienced attacks of h rpes than in those who had not had herpes before (Sutton BullUSAMD 3: 115 1944) Vaccination with smallpox vacci e prior to fever therapy did not prevent the development of postpyrexial herpes (Keddie et al. J 117: 1337 1941) The frequency of herpes following fever therapy is considerably less following a second pyrexia tha following the first (Warren et al. JExpM 71 155, 1940)

Herpes followed Salmonella food poisoning in 15% of the ca es (D Albora et al.: J 129 10 1945) It occurred in 33% of the cases, was often severe, and bore no prognostic significance in meningococcus meningitis, reported Harries (BMJ 423, 194.)

See d Morder ba J 111 2531, 1938), encephalitis with labial herpes Armstrong (PHRpts 58 16 1943) herpes virus in spinal fluid in case resembling lymphocytic choriomeningitis, Hamin and Rabens (JNeuropath 3 355 1944) meningoencephalitis Rivers (J 132 427 1946) herpetic encephalitis resembles that of lower animals, with numerous eosinophil nuclear inclusions Scott (NEngJM 250 183 1954) diagnostic technics and clinical varieties of herpetic infection, including skin, mucosal and ocular lesions, meningoencephalitis and generalized illness

Vesicular (Herpetic) Stomatitis.—Dodd et al. (JPed 12 95 1938) reported 88 cases in children of a disease which resembled aphthous stomatitis. The onset was sudden with fever and malaise Within 24 hours lesions appeared on the tongue, the inner surfaces of the lips and the buccal and sublingual mucosae, with swelling of the gums, pain on eating and cervical lymphadenitis. Herpes of the lip was present in 5 cases, and on the finger perhaps from autoinoculation in 2 The disease was self limited. Familial infections occurred.

Inoculations of the corneas of rabbits produced transferable purulent keratoconjunctivitis. Rabbits which survived infection were immune to further inoculations and were immune to herpes simplex too

Herpetic stomatitis is a highly infective but benign and uncomplicated disease occurring sometimes in epidemic form (Breese AmJDisChild 61 675 1941 Scott et al J 117 999 1941) The incubation period is from 5 to 7 days, and fever is marked Vesicles appear and become small ulcers with grayish bases on the fauces, palate and tonsils, and undergo evolution

and healing in due time Burnet and Lush (Lancet 1 629 1939) concluded that aphthous stomatitis in infancy is a common manifestation of primary infection with herpetic virus.

Herpangina so named by Zahorsky (SouthMJ 13 871 1920 AMediat 41: 181 1924) is the name preferred by Parrott et al (NEngJM 245 275 1951) who demonstrated 4 immunologically distinct viruses in 22 cases and found neutralizing antibodies against homologous strains of virus in all convalescent serums.

Adults are subject to herpetic aphthous stomatitis, the virus being demonstrable only while the aphthae are present (Rogers et al.: NEngJM 241 330 1949; Kilbourne and Horsfall AIntM 88 495 1951)

See Rochaix and Delbos (AnndeD 9, 169, 1938) aphthous fever with buccal and cutaneous lesions; Levine et al (J 112 2020, 1939) epidemic in summer camp; Burnet and Williams (MJAustral 1 63 1939) aphthous stomatitis and symbiosis of virus in man Cahn and Hart is (AmJOrthodont 28 140 1942) herpetic aphthae and rabbit cornea inoculations, immunity transitory; Anderson and Hamilton (MJAustral 1, 308, 1949), orphanage epidemic, antibody study children younger than 11 months did not become infected, subclinical infections; Huebner et al (J 145: 628, 1951) epidemic herpangina in Maryland, abrupt febrile onset, headache vomiting, sore throat, small ulcers in pharynx, virus identified as related to Coxsackie group A Sulkin and Stulberg (AmJDisChild 83: 421 1952) herpetic hepatitis; Buddingh et al (Pediat 11 595, 1953) recovery of herpes virus, demonstration of placental transmissions of neutralizing antibodies Kravis et al (Pediat 11 113, 1953), herpangina, Philadelphia epidemic of 1951, 3 types of Coxsackie group A viruses identified in stools and throats; Schlack (DeutschMWchs 78 213, 1953) coincidence of herpangina, poliomyelitis and Bornholm disease in Stuttgart in 1950; Nathanson and Mori (OralSurg MedPath 6 1284 1953) herpetic stomatitis associated with infectious mononucleosis.

Stomatitis and Diarrhea of Infants.—Diarrhea may be the serious manifestation of an epidemic of herpes virus infection. While stomatitis is usually present at the early stage generally about the anterior tongue regions, vesicles disappear within 24 hours, leaving a red and excoriated surface that heals only after a week or two and stomatitis may be quite mild or even overlooked (Buddingh SouthMJ 39 382 1946)

Vulvovaginal Herpes produces a typical clinical picture with symmetric, erosive lesions of the labia majores and minores, becoming tender ulcers with grayish yellow membranes. Painful for a week and similar to ulcus vulvae acutum (q v) it heals without scar Cases proved due to the herpes virus were recorded by Slavin and Gavett (PSExpBiol 63 343 1946)

Herpes Gestationis.—This resembles dermatitis herpetiformis (q v)

Recurrent Herpes probably is due to exacerbations of chronic herpetic infection. The lesions appear repeatedly at intervals of weeks or months in the same nerve region but not necessarily in identically the same spot. They may recur with the menses, and such cases may respond to the administration of estrogenic substances (Andersen abs YBD 1948 p 148) Herpes may follow trauma (Findlay and MacCallum Lancet 1 259 1940) While recurrent herpes was accepted as a virus disease the recurrences seemed to Blank and Brody (PsychosomM 12 254, 1950) to require a flaring factor which they thought sometimes to be of a psychiatric nature

Etiology —The cause of herpes is a filtrable virus. Supplemental factors which may provoke eruption are indigestion, febrile and toxic states, exposure to sunlight, and fever therapy The virus travels along motor sensory or sympathetic nerve fibers.

If the content of a herpetic vesicle is inoculated into the scarified cornea of a rabbit, there results keratitis which is transmissible and which travels by way of the nerves into the brain (Perdrau BJD 39 1 1927) its rate of travel from cornea to brain via the fifth nerve is constant and even (Doerr J 107 980 1936) Inoculation into the brain of the rabbit produces encephalitis, and the rod-shaped inclusion bodies measuring 0 1 to 0.2 by 0.3 to 0.5 micron in experimental herpes of the rabbit brain nerves and cornea are particles of virus (Nicolay and Kopciowska AnnInstPast 60 401 1938)

The chorioallantois of the chick embryo is infectible with the virus of herpes, although this does not affect the adult bird (Dawson AmJPath 9 1 1933) The chorioallantoic lesions show characteristic histologic changes, the epithelial nuclei undergoing enormous enlargement and trabeculation,

with fine basophile granules in the compartments. Virus isolation on the chorioallantois is aided by using penicillin 500u/Ml. and streptomycin 100 microgm./ml. to keep out contaminants without damaging the virus or the egg (Coriell et al JLabClinM 34 402, 1949)

Neutralizing antibodies, demonstrable by their inhibitory effect on chick chorioallantoic inoculations, are constantly present at a high level in individuals infected with herpes, and a heated preparation of the virus when inoculated intradermally provokes a specific erythematous reaction, regularly correlated with the presence of circulating antibodies according to Nagler (JImm 48: 13, 1944) Active immunity can be evoked in animals by the injection of sublethal doses of the virus (Rivers Filterable Viruses, Williams & Wilkins, 1928)

The virus was found to be present in the conjunctival secretion and saliva of patient with active lesions by Levaditi et al. (AnnInstPast 36: 63, 1922) but it apparently disappears between attacks of recurrent herpes (Hruszek: DWehn 90: 677, 1933) Electron microscopy studies showing the elementary bodies present in early lesions but absent from later lesions, were presented by Coriell et al. (JBact 59 01 1950)

The virus may persist despite high titer of antibodies in the host and carriers exist (Burnet and Lush: Lancet 1: 629 1939) Genital lesion in the female are not rare and the disease may be transmitted as a venereal infection (Sharlit: ADS 42 933, 1940) Antigenic dissimilarity of strain of herpes virus have been demonstrated by Jawetz et al. and by Womack and Hunt (Sci 120: 227 1954)

Complement fixation tests proved the separateness of herpes simplex and zoster to the satisfaction of Bedson and Bland (BJExpPath 10: 67 1929); see Dudgeon (JClinPath 3 230 1950); Gajdusek et al. (J 149 235 1952)

Human skin grafted onto the chorioallantois of the chick embryo is infectible with the herpes virus, which causes a vesicular lesion, while the lesion produced by infection with the zoster virus is pustular (Goodpasture and Anderson AmJPath 20: 447 1944)

Pathology—The vesicles are tough walled deeply seated and intra epithelial Eosinophilic inclusion bodies can be found within the nuclei of ballooned epithelial cells. Dense perivascular infiltration with small round cells underlies the vesicles and follows the vessels deep beneath the surface lesion This inflammatory reaction seems to provide fertile soil for cancerous proliferation, for neoplastic leukoplakia commonly invades at the site of labial herpes simplex. Epithelial cell smears from the vesicles of herpes simplex zoster and varicella show identical features which differ from those of any other vesicular disease (Blank et al J 146 1410 1951)

Diagnosis.—In vesicular contact dermatititis, the vesicles are close set rupture readily exude gummy serum, are associated with intense itching and are distributed on the skin without regard to the innervation. In impetigo contagiosa vesicles are discrete and autoinoculable develop serially and reach mucosae only by extension. Herpes genitalis may be confused with chancroid, and rarely with chancre In chancroid painful ulceration is always present and the lesions, while often multiple are never grouped as in herpes. The satellite lymph node of herpes is not abscessed. In syphilis the chancre is usually deeply infiltrated, lymph node involvement is almost invariable and dark field investigation is likely to reveal the spirochetes The satellite lymph node of herpes is larger and sorer than that of the syphilitic chancre

Prognosis.—The lesions take about 2 weeks to heal Recurrences are likely Herpetic encephalitis is a grave complication rarely met Secondary bacterial infection is possible and inept treatment often complicates and intensifies the disease before the physician sees it In severe cases scarring results.

Treatment.—All sources of irritation and focal infection should be removed in recurrent cases. Locally aluminum acetate 1:600 in water is comforting applied by means of a bit of cotton as a cold pack Spirits of camphor alcohol alone or with 0.2% zinc sulfate added or cologne water with 2% alum may be prescribed but camphor and strong mentholated ointments are in my opinion of little value if not irritant. Ammoniated mercurial ointment is harmful Aureomycin ointment seems helpful but Aureomycin has no influence in vitro or in vivo on the herpes virus, according to Baldridge

and Blank (PSExpB 72 560 1949) In a severe case with pain cortisone acetate 25 mg t.i.d. for 5 days affords good palliation. X ray therapy is advocated by some authorities 2 or 3 doses of 100 r may be given.

IMMUNIZATION —Freund (DmedWchn 54: 350, 1928) found that guinea pigs vaccinated against smallpox showed increased resistance to the herpes virus, and that patients with herpes had no further recurrences after such vaccination. Vaccination is now recognized as a means of preventing recurrences of herpes simplex; see Wise NYSJM 33: 1321, 1933); Foster and Abshier (ADS 36: 294, 1937); Davis (J 114: 2098, 1940) I have often cured recurrent herpes about the mouth by removing foci of infection, including malplaced third molars with pockets beneath them and by giving smallpox vaccine intracutaneously as recommended by Woodburne (ADS 43: 543, 1941) Vesicle fluid from the patient's early lesions was used as the immunizing antigen by Schmidt (ADS 32: 106 1935) Repeated injections of novocaine into the site of the lesion may prevent recurrences (Tzanck and Sidi: BsocfrançD 41: 1604 1934) Moccasin venom 0.. cc. of 1:3,000 dilution given subcutaneously each week, may work when vaccine fails (Fisher: ADS 43: 444 1941)

A peculiar repetitious spotty rash of the forehead and lips of a boy, impetiginoid and with crusting of the eyelids, was palliated by intracutaneous smallpox vaccination (Savitt and Ayres: ADS 60 633, 1949)

Kaposi's Varicelliform Eruption was originally described (1887) as a complication of infantile eczema. Pustulosis varioliformis acuta was the name given by Juliusberg (AfDuS 45 21 1898) Sudden in onset umbilicated erythematovesicular elements rapidly develop on the face and head especially and the neck sometimes on the elbows and wrists as well. The lesions become pustular desiccate and resemble those of chicken pox. Some scarring is usual. Fever precedes the eruption by 24 hours and persists for 1 or 2 weeks, falling by lysis. Differing from smallpox, new lesions may appear during a period of several days.

The disease is now recognized as herpetic, but it has been thought identical with generalized vaccinia (q v) which it certainly may resemble The fact that vaccination takes after recovery from Kaposi's eruption was reported by Freud (DWchn 98 52, 1934) Wenner (AmJDisChild 67 247 1944) and others.

There is some justification for taking the view that Kaposi's varicelliform eruption is a fitting clinical name for two different diseases, one being the result of vaccinal infection and the other of herpes (Whittle et al.: BJD 62 195, 1950; Sommerville et al. BJD 63 203 1951 Grist GlasgowMJ 34: 1 1953) for they apparently can be distinguished only by identification of the virus, just as streptococcic and staphylococcic impetigo can be positively identified only by cultures; see Anderson (BJD 61: 157 1949) on virus pyoderma. Generalized vaccinia occurs in persons with widespread dermatitis and in infants with eczema and it cannot readily be distinguished from Kaposi's eruption. But the virus of herpes has been demonstrated repeatedly and, while pathogenic cocci may also be found, Kaposi's disease is not vaccinia and may be defined as a specific, varioliform manifestation of herpes, according to Barton and Brunsting (PSMMC 18 199, 1943) Lane and Herold (ADS 50: 390, 1944) Lynch (ADS 51: 129 1945) and Lynch and Stevens (ADS 55 327 1947) Pepple et al. (SouthMJ 35: 667 1942) translated Kaposi's description in full.

There were 17 deaths among the 67 cases reviewed by Barton and Brunsting (ADS 50: 99, 1944) who demonstrated herpes virus in one of their patients. Of the 67 cases, 63 had atopic dermatitis, and 51 were 3 years of age or younger The 4 cases of Ruchman et al. (ADS 56 846, 1947) proved to be due to herpes virus, included 3 adults who had been successfully vaccinated against smallpox. The herpes virus has been demonstrated in many cases (Blattner et al. Sci 99 433, 1944 SouthMJ 4.: 812, 1949; Berke and Hallinger J 135 149 1947; Sims and French abs BJD 60 425, 1948, 9 cases with 5 deaths, and example of cross infection Wiley and Kletz BJD 61 166 1949 corneal ulcer; Baker et al. BMJ : 1334, 1952) A nurse contracted the disease from her patient, and the herpes virus was identified in both by Simpson (BJD 65 129 1953) In the course of an epidemic in children, several nurses contracted herpes (Brain AustralJD : 109 1954)

In treatment penicillin may be recommended only if secondary infection occurs along with such efforts as may be suitable in smallpox. Aureomycin topically and orally has seemed helpful to Baer and Miller (JID 13: 5 1949) Dareston and Carliner (JID 13 13 1949) Leier (ADS 63 456 1951) and McConachie and Anderson (BJD 63 307 1951) It was without benefit

in the case of Buerk and Blank (NEngJM 244 670 1951) Symptomatic therapy may include boric acid compresses and appropriate sedation. Cortisone is worth trying

Ulcus Vulvae Acutum.—The disease apparently an entity occurs in the form of vulvar ulcers in girls not exposed to venereal infection. Half the patients were virgins in the 20 cases of Olson (ADS 1: 279 1920) Flaherud (ADS 13: 55 1926) described the two types, gangrenous or severe and veneroid, which is more common. Compare Behçet's Syndrome, Vesicular Stomatitis, and Kaposi's Varicelliform Eruption.

Gangrenous.—The lesions are multiple but few in number located usually on contiguous aspects of the labia minora, accompanied by redness, swelling and burning pain. The onset is sudden, with fever as high as 40 C. The lesions are pea to dime-size round, with reddish areolae. The edges are soft and steep. The membrane covering the surface is thick or thin, gray yellow or bluish-black and firmly adherent to the base. It separates in 3 or 4 days, exposing the soft ulcer which has a smooth floor with a thin fibrinopurulent coating Fever and pain disappear at this time, and healing is complete in 10 days or so. *Sharply circumscribed, smooth, atrophic scars result.*



Fig 209 —Kaposi varicelliform eruption. (Brown BJD 46 L 1934)

Veneroid.—This resembles chancroid but Ducrey's bacillus is not present. Symptoms are mild. The tender ulcers are shallow and are located usually at the introitus. They vary in number and size. The edge is serrated and the shape rounded, oval, irregular or fissure-like New sores appear as old ones heal, so that the disease lasts a month or more. On the labia majora there may occur a miliary eruption of pinhead-sized lesions, with slightly elevated margins and depressed purulent centers, which persist only a few days. Smears reveal multitudes of *Bacillus crassus*, which closely resembles nonpathogenic *Lactobacillus acidophilus*. Virgins are the victims in 70% of the cases. Papuloerythematous or vesicular rashes, sometimes pustular of general distribution rarely accompany the disease.

Etiology —Factors capable of lowering the patient local tissue resistance hypothetically render the saprophytic *B crassus* pathogenic. The organism is perhaps identical with Doderlein vaginal bacillus and is ever present in the lesions existing as a thick (0.5 micron) and usually long (3 to 9 microns) *gram positive bacillus* with ends sharply right angled to its long axis. It is easily demonstrated in smear preparations from the ulcer sur

face. The identity of *B. crassus* Döderlein's bacillus and *Lactobacillus acidophilus* is likely according to Topley and Wilson (Principles of Bacteriology, Wood, 1937, p. 684); see *B. vaginae* Kruse and *B. crassus* in Bergey's Manual (Williams & Wilkins, 1948, pp. 362, 400). The significance of finding a luxuriant supply of a member of the vaginal flora in vulvar sores is highly dubious. The few cases I have seen looked like Kaposi's varicelliform eruption and ran the same course with abrupt onset, numerous discrete poxlike lesions, pain, fever and spontaneous resolution at the end of 10 days or so. Cases are rare, and opportunity to seek the herpes virus has not presented itself to me. Compare vulvovaginal herpes.

TREATMENT.—Weak antiseptics and rest suffice. No specific agent is known but the disease is benign and self limited. I should like to try cortisone for palliation.

See M. Donath (DJD 28: 286, 1924); Tsalov (ADS 30: 510, 1934); Popoff (DBoerfrangD 1938, p. 1264); Berlin (ADS 36: 69, 1939). There is no reference to an article on this subject in the Quarterly Cumulative Index 1946-1952, or in Excerpta Medica, section 13, 1948-1954.

HERPES ZOSTER

Symptoms.—Herpes zoster (shingles) is an acute virus infection of nerve structures manifesting cutaneous lesions in the form of groups of vesicles distributed along one or more peripheral sensory nerves. The disease occurs perhaps more frequently in individuals who are overworked, ill, or affected by the absorption of certain drugs, particularly arsenic, but it has been observed even in the newborn (Freud et al.: AmJDisChild 64: 895, 1942; Johnson: BMJ 1: 821, 1940). The appearance of the eruption is generally preceded by malaise of variable severity and by neuralgic pain or hyperesthesia in the affected region. The lesions are vesicles seated on slightly elevated erythematous plaques. They appear in successive crops along the course of the affected nerve. The number of patches is 1 or 2 to 12 or more. Each consists of half a dozen to a score of vesicles. In some cases, perhaps no visible lesions appear (see Segmental Neuralgia). In mild cases only a few lesions develop, the site of their location being hyperesthetic for several hours before they are manifested. They persist for a week to a fortnight, dry up, form crusts, and disappear. In severe cases involvement may be intense and extensive. The vesicles range from pinhead to pea-size and are usually filled with clear fluid. Their walls are comparatively tough. Their content may become seropurulent. Rarely the lesions are hemorrhagic. Gangrene may supervene due to either the severity of the disease or secondary necrotizing infection. In healing zona generally leaves corymbose, atrophic, white scars.

The disease afflicts approximately 2 per 1 000 population per year (Seiler: JHyg 27: 253, 1949). Small epidemics are common. During periods when the incidence of chicken pox is high, so is that of herpes zoster. The incubation period is between 1 and 2 weeks (Brostoff: BMJ 1: 790, 1955).

Any neural segment may be involved. Regional lymph node enlargement is usual. Pain is a variable symptom. In sturdy young persons the affection may give rise to little discomfort, but in elderly persons pain is generally a prominent feature throughout the attack, and neuritic sequelae are common (Hamilton: Pract 159: 122, 1947). The distribution of the eruption is practically always unilateral, although bilateral cases have been reported (Rattner: ADS 38: 436, 1938; Hailey: SouthMJ 47: 728, 1954). Occasionally the disease may involve widely separated regions at one time. It is common to find scattered varicelloid lesions over the trunk during the eruptive period (Grindon, Jr: ADS 39: 865, 1939; Barker: ADS 40: 974, 1939). The concurrence of varicelliform eruption with herpes zoster has an incidence approximating 8% of the cases, and has been interpreted as indicating a close relationship between zoster and varicella (McCallum: BMJ 1: 520, 1952).

In some 2,000 cases with lesions in over 2,500 segments, no sex or side preponderance was noted by Berggreen and Skjelo (DWch 106: 16, 1938) but the trigeminal and third cervical segments were the most frequent locations: trigeminal, 16%; cervical, 25%; dorsal, 48%; lumbar, 9%; sacral, 2%. Ophthalmic cases are rare in children (Bjork: Abs BJD 63: 199, 1951). See Katayama (Abs ADS 4_: 349, 1940).



Fig. 210.—Zona, right T 8 fourth day (Dr R. N Andrade.)



Fig. 211.—Herpes zoster left T 4



Fig. 212.—Herpes zoster



Fig. 213.—Herpes zoster early stage of eruption



Fig. 214.—Brachial herpes zoster with palmar lesions. (Dr J P Guequierre.)

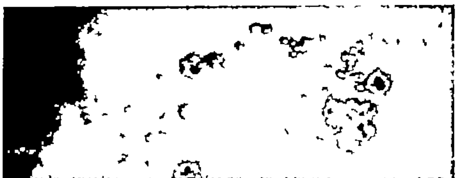


Fig. 215.—Herpes zoster involving right T 11, T 12, L 1 and L 2. (Dr Sam B Weidman.)



Fig. 216.—Herpes zoster early central gangrene.



Fig. 217.—Herpes zoster gangrenous lesions of back.

Fig. 218.—Supraorbital herpes zoster severe.

When zoster occurs in a patient with leukemia, especially lymphatic leukemia, nodules of leukemia cutis (q.v.) may appear in the herpetic dermatitis (Wile and Holman: ADS 42 587 1940)

Chronic recurrent herpes zoster is rare but indubitably is seen (Skoog: J 91 791, 1928) A patient of mine had a number of attacks in the second sacral distribution of his left thigh over a period of four years, during which the elimination of focal infection and

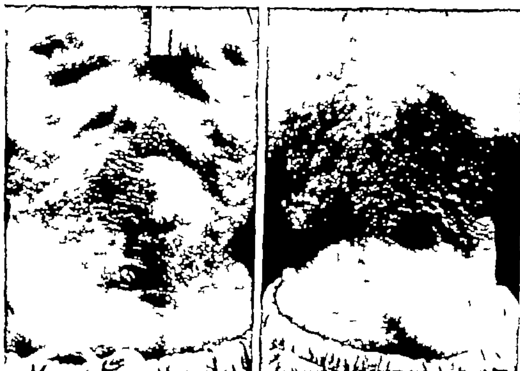


Fig 219.—Bilateral herpes zoster (Epstein and J cobson ADS 34 ### 1936.)



Fig 220.—Bilateral herpes (Dr Howard H ley)

repeated intracutaneous vaccinations with smallpox vaccine availed nothing In a woman I saw recently sacral segm nt recurrences were associated with distressing symptoms of cystitis, and these were ent rely relieved by cortisone.

Geniculate ganglion involvement, with ear pain auditory symptom and facial nerve palsy was described by Hunt (JNervMentD 34: 73, 1907) Involvement of th auricle may be associated with f cial palsy or Ménière s complex (Wakeley and M lvany: Lancet 1: 746 1939) Hunt s syndrome (aural herpes) is not necessarily du to geniculate

ganglion disease for cervical or other cranial nerve affection may cause otalgia, aural herpes and facial palsy (O'Neill: AOtol 42: 309 1945) Chronic otalgia may result (Bryan: WiscMJ 34 320, 1935)

Motor complications of zoster are neither rare nor remarkable and weakness of an upper extremity in cases of brachial plexus zoster may persist for many months (Taterka and O'Sullivan: J 122: 73 1943) Unusual cases exemplifying motor involvement were noted by Parkinson (BMJ 1: 8, 1949) Six cases complicated by Bell's palsy were reported by Spillane (BMJ 1: 236 1941) who thought that some cases of Bell's palsy are in fact geniculate ganglion herpes. Two cases of maxillary fifth nerve zoster followed in three weeks by facial paralysis were noted by Costello and Scott (ADS 60: 5?8 1949)

Unilateral tongue and palate involvement with impairment of gustatory sensibility was reported by Stepan (WienMWchr 103: 25? 1953)

Zoster involving the vagus nerve was described by McGovern (SouthMJ 44: 137 1951) Pain is confined to one side of the hypopharynx and larynx and to the homolateral ear nausea is a conspicuous feature; bradycardia and hiccough may be present. Dysphagia and extreme pain accompany herpes in the larynx.

Acute retrobulbar neuritis with sudden blindness, from which the woman recovered, occurred in a case of ophthalmic nerve involvement (Parry and Laid: BJOphth ?7: 467 1943)

Reported in herpes zoster have been myelitis (Whitty and Cooke: JNeurol 1 : 183, 1949); transient meningitis (Touraine: AnndeD 6: ?40 1935); lower motor neurone palsy (Carter: BMJ 1: ?34 1941); lower extremity weakness and loss of muscle stretch reflexes so as to simulate poliomyelitis (McIntyre: BMJ ?: 716 1951) encephalitis (Schmidt: DMedWchr 71: 308, 1947)

Etiology—A virus as the causative agent was long suspected but Fine (Filterable Virus Diseases in Man, Wood, 1932) stated that, while *transmission to man had frequently been effected, transmission to animals had been uncertain,* and filtrability had not been proved. Kundratiz (ZtschrfKinderh 39 370 1925) transmitted zoster to 14 of 22 children inoculated with vesicle fluid. Successful cultivation of the virus of herpes zoster was achieved by inoculating human tissue grafted onto the chick chorioallantois, by Goodpasture and Anderson (AmJPath 20 447 1944) see Blank et al. (PSExpB 69 341 1948)

The electron microscope reveals scanty but characteristic brick-shaped bodies in the fluid of early vesicles (Rake et al.: JBact 56: ?93, 1948) They closely resemble, but may be smaller than, those of varicella.

Arsenic may act as an exciting or supplemental etiologic factor (Knowles and Bolton PaMJ 41: 3 0 1938) Trauma as an inciting factor such as lumbar puncture, intramuscular injections, osteopathic manipulations and x-ray therapy, concerned Klauder (J 134 245 1947; ADS 64 407 1951) and Klauser (BJD 64: 224 195_) Zoster developing *after irradiation, especially in patients with cancer of the breast, occurred with greatest incidence some 3 to 6 months after treatment* (Ellis and Stoll: BMJ 2: 1323, 1949) Parfitt (BMJ 1 111 1936) reported the case of a person struck by lightning who developed zoster 14 days later Herpes zoster may appear during tabetic crisis (J 110: 67 1938)

A woman with Hodgkin's disease given nitrogen mustard developed zona, high fever and vesicular rash; she died, and at autopsy intranuclear inclusion bodies were demonstrated in various neural and visceral tissues by Cheatham (AmJPath 29: 401 1953)

Spinal fluid changes, motor neuron involvement, and encephalomyelitis, with their resultant symptoms, were discussed by Gais and Abrahamson (AmJMSc 197 817 1939) *Spinal fluid may show abnormality in albumin content, sometimes cells, increased pressure, and a right shift of the gold curve* (Schmidt: DWchr 100: 381 1935)

Herpes Zoster and Varicella.—The relationship between chicken pox and herpes zoster has received considerable attention. Some observers hold that *herpes zoster actually is an atypical manifestation of chickenpox virus. Traub and Tolmack* (NYSJM 31: 1072, 1931) believed that *evidence does not suffice to prove that the association is not fortuitous.* Zoster is not transmitted as is herpes simplex to the rabbit skin or cornea, and varicella does not immunize against zona, although the inoculation of zoster fluid into infants does indeed sometimes result in varicelliform eruptions (Brunsgaard BJD 44 1 1932) Chorioallantois inoculation experiments of Goodpasture et al. (Edit. J 126 898, 1944) indicate that the viruses are not identical. One finds numerous reports of the appearance of a case of zoster being followed by cases of varicella without other apparent contacts, such as those of Matheja (Arch J 114 2277 1939) and Garland (NEngJM 228 336 1943) and other reports of exposure to varicella being followed by zoster such as those of Kern (NJMSJ 42: 1 9 1945) and Horton (USNMB 43 74_, 1943) However when cases of zoster entered an isolated island community observed by Woolley (BMJ 1 802, 1946) *no varicella ensued.*

See McEwen (ADS 2 706, 1920); Roxburgh (BJD 39 12, 1927) Barrett (SouthMJ 31 193, 1938); Campbell (BJDisChild 38 31, 1941) Lynch (ADS 44 62, 1941); Platt et al. (JLabClinM 26 851 1940) Taylor (BMJ 2 388, 1946); Simpson (Lancet 2 1299 1954) varicella epidemic following zoster exposure, identity of viruses

Pathology—The vesicles, deeply seated and multilocular involve the lower rete and papillary layer The cavities are filled with serum, disorganized *prickle cells and leukocytes. Some degenerated epithelial cells* resemble protozoa and have been mistaken for parasites. Histologic changes in the cutaneous nerves can be seen after the 13th day of the eruption, comprising an irreversible degeneration with diminution of numbers of fibers in some bundles in the lower dermis (Ebert ADS 60 641 1949)

In the nervous system, histologic changes characteristic of zoster were found by Denny Brown et al. (ANeurP 51 216 1944) (1) ganglionitis showing necrosis and intense lymphocytic infiltration, with or without hemorrhage (2) poliomyelitis which is unilateral, localized and segmental and involves posterior horn and root; (3) mild localized leptomeningitis and (4) peripheral mononeuritis not only in the nerve distal to the ganglion but also in the anterior nerve root proximal and contiguous to the affected spinal ganglion.



Fig 111—Vesiculation of herpes zoster (Dr H. F Michelson.)

Diagnosis.—The neuritic distribution pain, and course of the eruption are distinctive. Prior to the eruption confusion with surgical disease can be embarrassing as in a patient who seemed to have a perinephritic abscess (*Bosher and Williams Surg 23 773 1948*)

Prognosis.—One attack usually confers immunity The disease runs an acute course, and the eruption heals in from 14 to 30 days. Hemorrhagic and gangrenous cases are serious. In supraorbital herpes zoster corneal damage sometimes occurs blindness may follow Scarring is variable. Bacterial secondary infection is possible and sometimes serious it is best prevented by keeping the lesions dry Neuralgia subsequent to zoster is sometimes enduring and extremely distressing especially in the aged, where pain seemingly irremediable can bedevil an old person into his grave It is usual however for neuralgia to fade gradually in a few months.

Treatment.—The administration of amidopyrine aspirin sodium salicylate codeine or Demerol gives symptomatic relief *Pain generally precludes* the patient s continuance with his work he is better off at rest, but if the

patient is getting off easy and so desires, he may do whatever is within his capacity for the disease is a self limited one presumably not hazardous to the public health.

Cortisone and ACTH give noteworthy relief (Nickel ADS 64 372, 1951 Poulin MaineMAJ 43 301 1952) Cortisone has become the mainstay of my treatment both during the acute stage and subsequently if neuralgia occurs. In adults who do not have peptic ulcer diabetes mellitus or tuberculosis I give 25 mg. with KCl 5 gr q i d. and feel that benefits are dependably conspicuous. Cortisone frequently dissipates neuralgia of a patient who is not seen until after his skin has healed, and the drug in such a case is given adequately but intermittently in amounts sufficient to control the symptoms. Favorable reports on the effectiveness of cortisone and ACTH in ocular herpes zoster include those of Doenges (IllMJ 106 131 1954) and Scheie and Alper (ArchOphth 53 38 1955) In postherpetic neuralgia which occurred in about a fourth of his patients Sauer (AD 71 488 1955) found the drugs effective in about 70% of the cases.

Comforting is a dusting powder freely applied and covered with a big snug bandage Melted paraffin may be applied as in the treatment of burns. Collodion, zinc stearate powder and cotton batting were recommended by Barney (OhioSMJ 39 42, 1943) Tense painful vesicles should be incised Radiant heat is often acceptable but hyperesthesia is characteristic in the affected region, and poultices, heat pads, ice bags and the like do not please the patient

Locally the use of counterirritation, such as ethyl chloride spray over the affected ganglion, has been recommended X ray therapy 200 r daily at 200 KV with 1 mm Cu filtration over the affected root ganglia for 4 or 5 days, is helpful best if started early (McCombs et al AmJMSc 200 803 1940) Intense ultraviolet erythema induced over the whole affected area stops pain A R. Taylor told me but I have not tried it.

Regional subcutaneous anesthesia with Novocain may be tried (Secunda et al. NEngJM 224: 501 1941) and hyaluronidase would probably simplify this. Injection of 0.5 cc. of 0 06% quinine and urea hydrochloride solution into the nerve so as to block it for a week gives prompt relief Lapp told me but Craig (PSMMC 11 677 1936) stated that even sectioning of the nerve may not relieve the pain. Findley and Patzer (J 128 1217 1945) preferred procaine infiltration of the appropriate sympathetic ganglion and described in detail the technic of paravertebral block, which does palliate in some cases (Rosenak Lancet 2 1056 1938) Postherpetic pain however remains unsolved by the neurosurgeon whose radical treatment, tried in desperation, may fail (Wartenberg J 134 94 1947)

Sulfonamides and antibiotics are without specific value but are needed if secondary infection appears.

Sodium iodide 1 0 Gm intravenously each third or fourth day for 3 or 4 doses, has been highly recommended (Ruggles ADS 23 472, 1931) 2 Gm given on the first, second fourth and seventh days was the dosage of Beers (J 112 2552 1939)

Pituitary extract given by injection occasionally relieved pain in a dramatic fashion (see J 115 2300 1940) The contraindications were coronary or myocardial disease hypertension and pregnancy (Somers and Pouppirt CalWM 42 370 1935) While pituitary was not infallible, it was dramatic when it worked (Gillett Lancet 2 307 1934) Ergot controlled pain in 17 of 30 cases of Combes et al. (JID 14 53 1950) Thiamin in 2 000-unit doses yielded only indifferent results in the experience of Rattner and Roll (J 112 2585 1939) Liver extract given because it was the only medicine available helped the prisoner-of war patients of Diekle (BMJ 1 942, 1946)

Biologicals which have been used with avowed good effect include convalescent blood (Gunderson AOphth 24 137 1940 Becker ADS 58 265 1949) gamma globulin (Grua DMedWehn 77 1074, 1952) autohemotherapy (Jones and Alden SouthMJ 30 735 1937 Poth ADS 60 636 1949); diph

theria antitoxin (Walker and Walker AOphth 20 304 1938) moccasin venom (Dennie and Morgan JID 12 153 1949) smallpox vaccination (Tillie NYSJM 43 857 1943) gamma globulin, 10 c.c. initially and 5 c.c. every other day thereafter (Weintraub J 157 1611, 1955)

FOOT AND-MOUTH DISEASE

Symptoms.—Foot and mouth disease is an epizootic infection of cattle, hogs, sheep, goats and other animals man being occasionally attacked. The virus is present in the fluid of the vesicles. Inoculation occurs through abrasions of the skin and mucous membranes. The disease was prevalent among the flocks and herds of England in the latter half of the nineteenth century and many cases of stomatitis were attributed to it (Arkwright: Lancet 1: 1191, 1928)

In man, the incubation period ranges from to 5 or even 10 days. The onset of an attack is usually attended with constitutional symptoms of moderate severity and a feeling of dryness and burning in the mouth. The buccal mucosa becomes congested and swollen Within * or 3 days small vesicles develop on the lips, tongue and pharyngeal walls. The manifestations of constitutional disturbance gradually subside After 48 to 7 hours the vesicles rupture spontaneously, leaving reddish extremely tender ulcers. The individual lesions are from 3 to 10 mm. in diameter They at first contain clear watery fluid, but secondary pyogenic involvement is common. The regional lymph nodes are swollen and tender The ulcers usually heal promptly with little or no scarring (Sutton and O'Donnell J 66: 947 1916) Nonfebrile disease limited to the oral cavity is probably not foot and mouth disease which evokes primary vesicles at the port of entry with later generalization. Cases of proved human infection were reported by Arocha (MedMex 27 163, 194) and Rille (DWchn 110: 146 1947)

Etiology—Loeffler and Frosch (ZentralblfBakt 23 371 1899) attempted to free the vesicular lymph from corpuscular elements by passing it through Berkefeld filters; they discovered that the filtrate was as actively provocative of the disease in cattle as was unfiltered material. This was the first time animal disease had been shown to be due to a filtrable virus. Pape and Waldmann (BerltierarzWchn 3 : 349 449 1921) reported the successful transmission of the disease to guinea pigs by inoculation of the volar skin. Following this the animals became immune to that strain of the virus. This procedure is the customary diagnostic test; *it may not be performed in the United States without special permission from the Bureau of Animal Industry permission which is not given except to State and Federal veterinarians.* In Great Britain, permission must be had of the Ministry of Agriculture.

There are three types of virus, A B and C, which do not show cross immunity (Waldmann abs YBD 1937 p. 196 Wagener: abs J 110 1409, 1938) and the disease has been transmitted experimentally to man. The virus is very minute (Schlesinger and Galloway JHyg 37 445 463, 193 ; Elford and Galloway BJExpPath 18 155 15 1937)

The virus survives quick freezing, which prevents the acidification of rigor mortis, and survives in frozen liver kidney and lymph nodes of diseased cattle, so as to be infective to swine under experimental conditions (Henderson and Brooksby: JHyg 46: 394 1948)

Treatment.—The course is self-limited. Treatment is symptomatic. The Waldmann vaccine prevents the disease in cattle (Rushmore BullUSAMD 3: 94 1945)

WARTS

Warts are small circumscribed, autoinoculable epidermal and papillary growths. Several clinical forms are recognized

Verruca Vulgaris is the common type. This kind begins as a tiny circumscribed grayish epidermal thickening The lesions are single or multiple and become pinhead to pea size, rounded papilliform excrescences. In color they are grayish yellowish or brownish. They give rise to no subjective symptoms. The lesions are usually discrete but may coalesce forming rugose plaques. Although the dorsal surfaces of the fingers hands, and wrists are the sites of predilection, no region is exempt.

When the wart is shaved in the plane of the skin, radiating brown structures which are hypertrophied papillae become readily visible against the background of translucent calluslike epithelium (Corson UCutRev 38 120 1934) The hyperkeratotic material interstitially located between the papilla may be macerated or chewed away by a child, and a digitate or filiform effect produced. Beneath the hyperkeratotic surface of a large wart the epithelium is altered and becomes towlike and pasty Using cautery or desiccation treatment, one must wipe the corium bare of this to cure

Warts about the nails are often difficult to eradicate. The hyperkeratosis and elongation of papillae produced by the verrucous process are recognizable.



Fig. 222.—Verrucae vulgares, with involvement of nail folds.

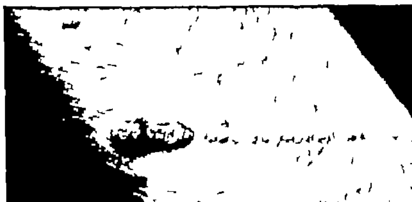


Fig. 223.—Warts on forearm, showing linear autoinoculation. (Dr J. Lame Calloway.)

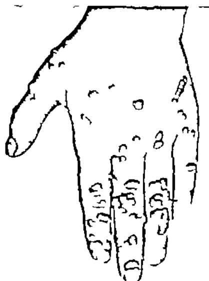


Fig. 224.—Verrucae vulgares.



Fig. 225.—Filiform warts.

Warts may involve the folds of the nail sometimes encircling it, even pushing beneath it Such lesions may be quite painful and of confusing clinical appearance Picking at them and manicuring lead to their perionychial dissemination. See Montgomery and Culvert (ADS 10 425 1924)

Warts of the eyelids may provoke conjunctivitis and keratitis as molluscum contagiosum does (de Rotth AOphth 21 409 1939)

Verruca Plantaris.—Lesions of peculiar aspect result when the soles are involved. They are called stone bruises by the uninformed This is a com



Fig 226—Plantar wart. (Dr Clyde L. Cummer)
Fig 227—Plantar warts macerated by salicylic acid plaster



Fig. 228—Plane warts, face

Fig. 229—Plane warts, hand.

mon condition epidemics in schools being seen (MacKenna BMJ 1 509 1938) The lesions are frequently located under the second metatarso-phalangeal joint or on the heel. They resemble small, oval calluses. They are sensitive, causing pain like a thorn in the foot When the overlying epidermal lid is removed, a well like cavity, partially filled with moist, tough tow colored corneous material, is exposed and tender bleeding tips of the hypertrophied papillae become apparent They are carefully to be distinguished from calluses (Montgomery and Montgomery J 124 756 1944)



Fig. 230—Condyloma acuminatum. (Dr Sam Sheltzer' patient.)
Fig. 231—Condyloma cuminatum, perianal (Dr Osw ld G Costa.)



Fig. 232—Cornuat warts of prepuce



Fig 233.—Filiform wart t the naris.

Spontaneous regression of plantar warts, not those of the mosaic type was described by Rasmussen (ActaD-V 34 144 1954) This apparently took place in about 3% of more than 5 000 cases. Warts in regression became dark, perhaps black the surface dry the periphery perhaps scaly the wart material crumbly and the underlying papillary vessels black because of thrombosis. The phenomenon was more common in children than in adults.

Mosaic Warts.—Large composite patches of warts are seen fairly commonly on the sole These are characteristically spread over a large area, are dry comparatively painless, progressive and radioresistant. They are difficult to cure See Montgomery and Montgomery (NYSJM 37 1978 1937 ADS 57 397 1948)

Papillomas with Pearly Bases and erythematous halos lacking the hard hyperkeratotic top and surrounding callus of the ordinary wart were segregated as a special clinical type by Straus et al. (PSExpB 72 46 1949; JID 15 433 1950) They demonstrated in the lesions, obtained from the palms and soles of children spherical, viruslike particles of crystalline appearance which tended to aggregate in regular nets. The lesions were easy to remove with a curette. Pyknotic nuclei were numerous in the lower layers of the thickened epidermis, and intranuclear round eosinophilic inclusion bodies occurred in the Malpighian cells immediately external to the basal layer The elementary bodies resembled but were much smaller than those of molluscum contagiosum.



Fig 234.—Verruca simulating early squamous carcinoma. (See Fig. 235.)



Fig. 235.—Verruca, section of lesion seen in Fig. 234.

Verrucae Planae.—Flat warts are small polygonal, yellowish or brownish pinhead to pea size flat or dome topped growths which develop especially on the face forehead and dorsal surfaces of the hands. They may be discrete but are usually grouped and may coalesce They are asymptomatic but are quite resistant to treatment These are often disseminated by cold cream and hand lotions. A pigmentary form simulating *seborrheic keratoses* was observed by Becker (ADS 34 265 1936)

Verruca Digitata.—This variety which occurs most frequently on the bearded region and scalp is characterized by its architectural scheme being composed of filiform projections with pointed horny caps, closely grouped on a narrow base.

Verruca Filiformis.—This is a small slender flexible, threadlike growth covered with smooth epidermis. The sites of predilection are the neck and the eyelids, and the bearded area in men whose shaving inoculates and disseminates them widely. A filiform wart on the nose of a newborn was seen by Ronchese (ADS 65 231 1952). Multiple lesions resembling filiform warts about the corona penis produce a curious appearance descriptively named hirsuties papillaris penis (Wigley and Haber BJD 61 427 1949 Tomlinson BJD 61 429 1949). See Winer and Winer (Trans. Western Sect Amer Urological Assn., July 1955).



Fig. 236.—Mossy foot.



Fig. 237.—Warts causing mossy foot. (Costa ADS 53 644, 1946.)

Lymphostatic Verrucosis (Mossy Foot)—Verrucose change accompanying chronic edema has been recognized for many years pointed out Loewenthal (J 152 475 1953). The name mossy foot was given by Thomas (AnnTropM 4 95 1910). Cases were reported by Loewenthal (Ann TropM 28 47 1934) who was convinced that elephantiasic lymphostasis was the cause. Some 200 cases were described by Clark (TransRoySocTropM 42; 287 1948). The condition responds to firm prolonged pressure by elastic bandages. Treatment with measures usually employed in attacking common verrucae failed in the case affecting an amputation stump reported by Schamberg (J 150 1653 1952). Compare chromoblastomycosis and elephantiasis.

See Per Letter Crumder (J 155 1000 1954), Hales (J 156 874 1954) Loewenthal (J 155 1827 1954) priority of name [illegible] D [illegible] (AD 71 644 1955) case, obese female.

Verruca Acuminata.—This variety also known as condyloma acuminatum or incorrectly venereal wart develops on moist tissues near the mucocutaneous junctures. The formations consist of closely aggregated pointed tufted or pedunculated pinkish or purplish projections, of variable length and consistency. About the vulva or beneath the foreskin they may vegetate become covered with pus, and stink with macerated epithelium and decomposing secretions. They are autoinoculable seldom disappear spontaneously and are transmissible to the sex partner (Barrett et al J 154 333 1954 Ronchese ib p 1198 Squires J 155 511 1954) Despite sex transmission *the disease should not be considered venereal (Edit AmJSyph 38 609 1954)* Anal mucosal lesions were present in the patient with anal condylomata *observed by Chester and Schwimmer (AD 71 149 1955)*

Etiology.—Wile and Kingery (J 73 790 1919) inoculated warts successfully by intracutaneous injection of bacteria free filtrate of wart material Templeton (ADS 32 102, 1935) obtained takes as long as a year after inoculation. *An epidemic of warts among a group of employees was shown by* McLaughlin and Edington (Lancet 2 685 1937) to have been due to contaminated glue Warts can be spread by ointments.

Warts occur in practically all of the familiar animals, and in cattle sometimes attain a *remarkable degree of severity Immunologic therapy, effective in treating cattle* is of dubious value in human infection but Biberstein (ADS 50 1, 1944) reviewed pertinent literature described a method of preparing vaccine, and claimed to have cured 60% of his cases of vulgar and plane types.

A filtrable agent was grown in the chick embryo inoculated with macerated, filtered material from a verruca vulgari by Blvins (JID 70: 471, 1953; Sci 117: 300, 1953) Tiny hard, whitish pearls developed on the chorioallantois. It was Waelsch (AfDuS 124 625, 1918) who showed that inoculation of an extract of condyloma into human skin produced the common wart while inoculation into a mucous membrane resulted in condyloma.

In rabbits, in which the Shope virus produces papillomas that have received intensive study because of their tendency to become malignant, Kidd (JExpM 65: 703 1938) observed that immunologic reactions to this virus are similar to those of classic immunologic antigens. Shope papilloma virus took embryo rabbit skin transplanted in species resistant to the infecting agent reported Greene (CancRes 13: 59 1953); see Carcinoma, etiology virus.

See also Asbestos warts. The prick of a thorn is often alleged by the patient *to have infected his wart. A tiny wart feels subjectively as if it contained a foreign* bod

Pathology.—The first stage of the development of verrucae is characterized by localized acanthosis with hyperkeratosis. Underlying papillae are *lengthened and the papillary body is stretched and flattened* Some papillae are *thinned and elongated. Epidermal cells infected by the intracellular parasite* undergo degenerative changes. In the juvenile wart marked hyperkeratosis is absent but the epidermal cellular alteration is present.

Meticulous observations of the keratohyaline changes were reported by Meirowsky et al (BJD 60 275 1948) The only changes in individual cells distinctive of verruca were found in the nuclei (Blank et al. JID 16 19 1951) and cytoplasmic bodies were deemed nonspecific. Early changes in the deep layers become more marked as the cells move toward the surface and culminate *with complete filling of the nucleus with inclusion material, so that it* is two or three times the size of a normal nucleus its fine structure being replaced with a dense homogeneous mass. Mature inclusion filled nuclei are easy to see even at low magnification as dense ovoid bodies likely to be surrounded by ballooning degeneration such as is found in other virus diseases of the skin The inclusion material is rich in nucleoprotein, apparently of the desoxyribose form.

Some warts contain inclusion bodies and others do not, according to Lyell and Miles (BMJ 1 912 1951) Warts with inclusion bodies (type I for inclusion) are usually volar or paronychial. Those without (type B for banal) are verrucae vulgares, and mosaic warts are of this kind They would limit the name verruca vulgaris to warts lacking inclusion bodies, while those with inclusion bodies they would call myrmecia after Celsus.

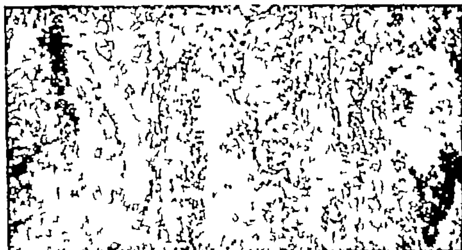


Fig. 238.—Verruca vulgaris (× [illegible]). Distention of nuclei with basophilic inclusion material begins in deeper prickle cell layers. Large dense fully formed "inclusion bodies" are surrounded by a clear zone of "ballooning degeneration." (Blank et al.: JID 16: 19, 1951.)

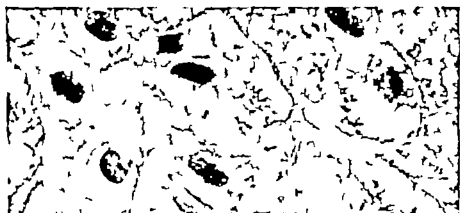


Fig. 239.—Verruca vulgaris (×[illegible]). Cells containing densely filled nuclei ("inclusion bodies") possess degenerated, swollen cytoplasm. (Drs. H. Blank, M. Buerk, and Fred Weidman.)

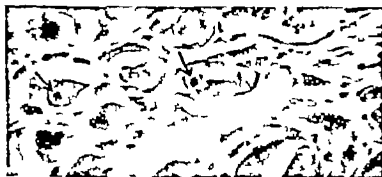


Fig. 240.—Verruca vulgaris (×[illegible]). No diagnostic "inclusion bodies" are seen. Arrows indicate large nucleoli indicating site of synthesis of nucleoprotein. Dense masses of keratohyalin, various in size, may confuse. (Blank et al.: JID 16: 19, 1951.)

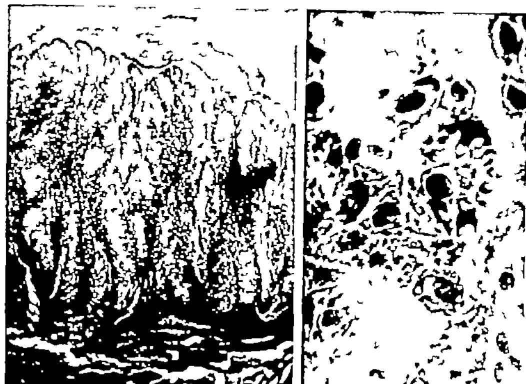
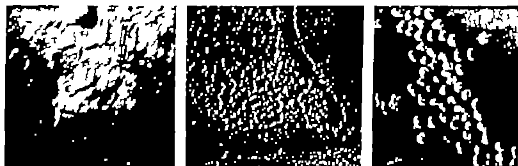


Fig. 241.—Papilloma yielding viruslike particles, ×30. (Strauss et al. PSExperBiol 72 46 1949.)

Fig. 242.—Papilloma tissue (×1200) from Fig. 241. Not round, solitary intranuclear inclusion bodies not so dark as adjacent irregular chromatin masses. Solid cytoplasmic bodies are evident. (Dr. M. J. Strauss and collaborators.)



Figs. 243 and 244.—Electron micrograph (×11 400) of viruslike particles from papillomas with intranuclear inclusion bodies. Preparations are from 1 patient. (Strauss et al. PSExperBiol 72 46, 1949.)

Fig. 245.—Elementary bodies (×11 400) from molluscum contagiosum. (Strauss et al. PSExpt Biol 72 46, 1949.)

Diagnosis.—Ordinary warts are familiar. The plantar type may be confused with corns but can be recognized by shaving off the superficial layer so as to expose the papillary tips. Juvenile warts are distinguished from lichen planus by their color, distribution and lack of pruritus. Early squamous carcinoma (q.v.) is often wartlike. For differentiation from epidermodysplasia verruciformis (q.v.) see Waisman and Montgomery (ADS 45 259 1942). A plantar wart is an ordinary wart pressed into the cutis, and calluslike hyperkeratosis surrounds it.

Prognosis.—Warts are benign but are liable to infection Plantar warts are painful even incapacitating Verrucae involving the nail folds are resistant and difficult to treat. Individuals differ in vulnerability to wart infection and an untreated wart persists on the average some 2 or 3 years then heals spontaneously Rulison found (ADS 46 66 1942)

Treatment.—For oral administration no remedy is reliable Injections of bismuth and of normal saline were equally effective in the experience of Goodman and Greenwood (ADS 30 659 1934) Bistrimate 2 tablets 3 times a day which may intoxicate cured 8 of 14 cases of multiple warts for O Connor and Tweedall (JMoMA 45 25 1948) Vitamin A 100 000 units a day by mouth may cure (Fisher and Chamberlain PaMJ 51 151 1947) Methionine 2 Gm. per day cured 2 patients of Merklen (PresseMéd 64 284 1954) Subcutaneous injections of the Shwartzman typhoid bacillus filtrate gave outstanding results as reported by Jacobi et al (UCutanRev 43 274 1939)

Using mechanical methods, an anesthetized lesion can be scraped out Cauterization with dichloracetic acid, acid nitrate of mercury or similar caustics may be used. Any means of blistering will serve if used with skill including solid CO (Holdin Davis BMJ 2 18 1938) An annular wart resulted when vesiculation with cantharides cured only the central portion in a patient of Lewis (ADS 51 66 1945) Fulguration is a rapid, clean, efficient procedure An electrosurgical cutting technic was described by Karp and Frank (ADS 45 728 1942) One should destroy only epithelium and those elongated papillae which project above the niveau so avoiding scar Epidermis must be sacrificed to a distance of 2 or 3 mm peripherally to reduce the likelihood of recurrence After healing though there is no scar depigmentation results and may be conspicuous in brunets.

One may inject a few drops of Iodobismitol into the base of the wart (Shellow IllMJ 66 332, 1934) Quinine and urethane 50% urea, sodium morrhuate or potassium oleate may be used similarly (MacKay ADS 41 736 1940)

Occlusion obtained by tightly binding elastoplast over the warts and redressing once a week may cure (McAusland BMJ 1 1123 1935) Occlusion by adhesive tape after a preliminary application of trichloroacetic acid or phenol was recommended by Frank (ADS 65 617 1952) Outstanding success in treating periungual warts, which may be considered difficult indeed was claimed by Halpern and Lane (JMoMA 50 765 1953) by applying 80% aqueous monochloracetic acid, then covering the lesions with 40% salicylic acid plaster trimmed just a trifle larger than the wart pressed on, and left in place for from 3 to 4 days. A similar method using trichloroacetic acid was recommended by Prazak and Lazar (ADS 69 230 1954)

Formaldehyde 3 or 4 cc. in half an ounce of Aquaphor can be applied twice a day to the wart, which hardens, is shaved off weekly and may eventually disappear (Lynch and Karon ADS 62 803 1950) Formaldehyde commercial 40% a teaspoon to the quart of water is useful for daily foot soaks in treating mosaic warts. Freezone containing zinc chloride salicylic acid, castor oil alcohol and ether has considerable usefulness in dealing with warts, corns, soft corns and calluses.

Individualization of treatment of the lesions was stressed by Burrows (BJD 55 60 1943) and Lane (J 144 1361 1950) in papers which discussed the treatment of warts comprehensively

Radium is a useful tool. An applicator of 5 mm diameter containing 5 mg of radium delivers a dose just short of vesiculating when applied in close contact without filtration for about 10 minutes. It is especially helpful in dealing with small warts located where an electrosurgical procedure would make an undesirable wound

X ray therapy is excellent if used with skill The curative dose is given in one dose (Pipkin et al. SouthMJ 42 193 1949) After shaving off the

excess corneous material the wart is accurately shielded so as to expose a margin of about 2 mm A dose of something like 1 400 r at 100 KV no filter added is administered. Small warts require a larger dose, and large areas should receive somewhat less. Reaction is apparent after about 12 days but is mild consisting only of slight tenderness, swelling and erythema. This fades, and the wart comes to resemble the translucent corneum of a healing blister About 40 days after the dose the wart is ready to peel off It may do so spontaneously but if it is not peeled off the virus, unaffected by the x ray infects the new epithelium beneath. Therefore the patient is emphatically requested to return on or about the fortieth day after x ray treatment so that débridement may be performed by the physician. This essential second visit changes the statistics of cures obtained from about 70% to nearly 100% Having once given an area a large dose of x ray therapy such treatment may not be repeated without causing radiation atrophy See Sutton (GI 2 19 1950) Oliver (ADS 42 302 1940) Montgomery and Montgomery (NYSJM 41 371 1941) Contact therapy with low voltage was recommended by Thomsen and Rauschkolb (ADS 65 553 1952)

Suggestion therapy by psychiatric means has a large literature and undoubtedly is effective in a fair proportion of cases. The methods of folklore include such measures as rubbing the wart with some curious substance removing the mother wart plucking a hair for each wart and burning it tracing the region on paper and burning that etc (Sulzberger and Wolf MRec 140 552 1934) The practitioner of suggestion therapy must believe that it will work and convince the patient that this is so see Bloch (KlinWchr 6 2271 2320 1927 Vollmer PsychosomM 8 138 1946 Bett Pract 166 77 1951 Allington ADS 316 1952) Obermayer reported a success with hypnosis (ADS 60 1222 1949)

VERRUCAE PLANAE —A single accurate careful application of Vleminckx solution may suffice The cautery can be used with suitable accuracy Cannon (ADS 49 66, 1944) recommended the ethyl chloride spray and curet followed by 50% phenol wiped off with alcohol.

MOSAIC WARTS may respond to 60% salicylic acid paste carefully delimited in its application and occasional painting with strong silver nitrate solution (the Montgomery ADS 45 1023 194) Thompson (BJD 55 307 1943) advised soaking the lesion for 10 minutes each evening in 3% formol. The white macerated plugs that develop should be débrided and the treatment persisted with for the 3 to 8 weeks required for cure

PLANTAR WARTS.—Dependence is placed mainly on x ray or radium No filter is employed Radon 16 millicurie hours filtered with 0.3 mm of steel 1,200 to 1 900 r single dose was recommended by Mark and Friesen (NEngJM 223 851 1940) If a single dose of 3 to 5 E does not cure although it does in about 9 of 10 cases some other attack should be undertaken. Electrodesiccation and electrocoagulation are preferred by many Electrosurgical methods have been given in detail by Lewis (NYSJM 33 1 1933 Frank ADS 45 439 194 Karp ADS 53 496 1946) Using local anesthesia all verruca bearing epidermis is completely separated from the dermis. The second degree burn is dressed with a bland, antiseptic grease such as Aureomycin ointment. The actual cautery may be so used with satisfaction in dealing with large warts. Blistering adequate to cure may be accomplished by the firm application of solid carbon dioxide for 3 minutes after Windemuth (Crow and Scott Lancet 2 31 1934); I have not tried this.

The curett with local anesthesia was recommended by Beale and Richardson (Ho thMJ 49 573 1953) Bleeding is profuse but the application of Merthiolate an antibiotic ointment and pressure dressing is followed by cure in most instances the stated)

One may pare the wart use a ring pad and salicylic acid ointment and treat the lesion successfully with phenol and t l ed accomplishing a cure by chemical cauterization (Black ADS 56, 430 1947) It is possible to use podophyllin in conjunction with paring and occlusive dressing so as to achieve a cure though this is not the easiest way (Kurtin and Wetter ADS 57 303 1948 W L ADS 63 490 1953)

Injection of various chemicals to the base of the wart may prove successful. Aqueous bismuth solution has been so used Simply Novocain may be effective (Jim son and Rhea N E gJM 49 631 1933) The injection should be made at the stratum germinativum t and, although this would be technically hard to achieve The injection must influence the dermoepidermal junction for it to be effective One half per cent phenol, although it hurts a bit at first can be used in this way (Anning Lancet 1: 976 1948 Hemphill BMJ 1 71 1933)

Euphorbium resinifera commonly known as wart weed was tried by Goldblum and Curtis (JID 20: 43 1933), who reported that the 30% alcoholic solution produced lysis of rete cells in human and guinea pig and, when applied to plantar warts, cured 59 of 60 cases within 4 months. Less enthusiastic was the report of Martin-Scott (BJD 60: 5 1954)

Each wart should be treated individually. Surgery is not the first but the last resort in treating plantar warts, for they are likely to recur in the scar of an excision wound. Plastic surgery is required when a plantar wart has been mistreated, particularly with x-ray therapy, and this is by no means a rarity (Brown et al J 108 4 1937; 146: 623 1951; Shaw: BMJ 1: 11 1948). Amputation of the plantar condyle of the underlying metatarsal head was recommended in some cases to relieve pressure by DeVries (J 1[illegible]: 1902, 1933)

ACUMINATE WARTS AND CONDYLOMATA respond in a gratifying way to podophyllin. This resin 25% in liquid petrolatum was reported efficient by Kaplan (NOrMSJ 94 388 1942): a single application meticulously applied only to the moist warts being followed by considerable inflammation and then exfoliation. Culp and Kaplan (AnnSurg 120: 251 1944) confirmed this observation, noting that, of 200 cases 8_% were cured with one application and all were cured by a few subsequent applications. Cohen (Pract 156: 133, 1946) warned against transferring the agent to places where it is not desired. Sullivan found 20% podophyllin in alcohol preferable and Mark (JMoMA 44: 749 1947) recommended 15% in compound tincture of benzoin, for it stays where it is put. The use of 1.5% podophyllin in polyethylene glycol to be applied daily by the patient is safe reliable and less painful than the strong concentration (Warner DWebu 1 1: 178 1950); 3% seemed a more satisfactory strength to Scott (BMJ 2: 297 1954)

Podophyllin must not get into the eye, for it would cause severe and serious conjunctivitis. Its effect, Sullivan and King (ADS 56: 30 1947) discovered, much resembles that of colchicine. Podophyllotoxin is the active ingredient of the resin (Sullivan et al: SouthMJ 41: 336 1948). Alpha and beta peltatin are also effective (Sullivan and Hearin: ADS 66: 706 1952). Violent reaction necessitating a dorsal slit may follow the use of podophyllin beneath the foreskin; the patient should be circumcised first (Finkle and Frishwasser JID 8 190 1947)

The chemical is useless in treating verrucae vulgares (Frank and Cohen: ADS 56 109, 194). A review of its dermatologic applicability was given by Nelson (ADS 67: 458, 1953). Unusual pseudoepitheliomatous reactions to podophyllin were seen by Maxwell and Lamb (ADS 70: 510, 1954). Toxic encephalopathy apparently due to podophyllin was fatal in a pregnant Negress whose huge vulvar lesion was treated with the drug (Ward et al SouthMJ 47 1204, 1954)

Repeated painting of moist lesions with Fowler's solution has effect comparable with, but gentler than podophyllin according to Pa losky and Leider (JID 13: 73 1949)

MOLLUSCUM CONTAGIOSUM

Symptoms.—Molluscum contagiosum ("water wart") is a virus disease of the epithelium characterized by small waxy globular tumors which generally show tiny rounded concavities at their apices. The lesions range in size from pin point to pinhead and develop slowly. At first they are acuminate or globular in shape with broad bases, but as they grow larger they become flattened and umbilicated. The number of lesions is from 2 or 3 to 20 or more. The mucous surfaces, particularly the borders of the lips and lids, are occasionally involved. Lesions of the eyelids may provoke mild conjunctivitis. The lesions are at first firm but become somewhat softened and ultimately may suppurate, finally healing without scar. Sometimes the tumors disappear spontaneously but if untreated generally persist for many months. The lesions are discrete and may be grouped. They give rise to no symptoms unless inflamed. Numerous and minute miliary mollusca resemble verrucae planae (Beehet ADS 37 897 1938)

Etiology and Pathology.—A like disease occurs in birds, "fowl pox," and in animals. It is autoinoculable and contagious. Juliusberg (DeutschMWchn 31 1598 1905) demonstrated the filtrable nature of the causative agent in human beings. Successful human inoculations with sterile filtrates were obtained by Wile and Kingery (JCutD 37 431 1919)

Strongyloplasma hominis is manifest as spheric particles which are 0.25 micron in diameter, numerous and nonmotile in fresh preparations (Lipschutz AfDuS 10 : 237 1911). Aggregates of them form acidophilic inclusion bodies within the cytoplasm of



Fig. 246.—Molluscum contagiosum. The largest lesion is uncommonly large. The central puncta are plainly shown. (Dr. F. Ronchese.)





Figs. 247 and 248.—Molluscum contagiosum.

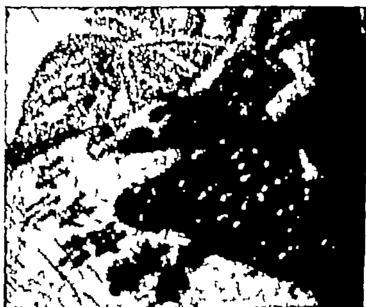


Fig. 249.—Molluscum contagiosum inoculated by tattoo 6 weeks previously. (Dr. John Butler.)

infected epithelial cell The lesions are formed by hyperplasia of infected epithelial cells. Cytoplasmic inclusions push aside the nuclei and bulge the cell walls (Melrowsky et al.: JID , 105, 1940) Fragment of a inclusion body i fowlpox were proved to be infectious by Woodruff and Goodpasture (AmJP 6: 713, 1930) Intracerebral inoculation of the virus in chicks produced a characteristic and fatal disease (Buddingh: JExpM 67 9?1 933, 1938) An attack of molluscum contagiosum does not confer immunity and while its virus and that of birdpox are similar the two diseases are quite different (Low: EdinMJ 53: 657 1946)

Diagnosis.—The size color appearance and recent acquisition of the lesions, together with the fact that their contents can be squeezed out are distinctive Fibromas, milia comedones and verrucae are to be excluded. Mil



Fig. 250.—Molluscum contagiosum. (Schiff and Ronchese RhodeIsMJ 30 600, 1947)



Fig. 251—Molluscum contagiosum, microdissection of infected epithelial cell. (Van Rooyen JPathBact 46 425, 1938) *A* One needle in cell to steady it, other in molluscum body *B* Molluscum body moved slightly both needles in focus. *C* Molluscum body taken from bed, which remains a cavity

lary cases are sometimes confusing but careful study of the lesions with a hand lens should clarify the diagnosis. Large solitary lesions sometimes resemble carcinoma (Tobias ADS 64 208 1951) Inflamed lesions of the lid margins may simulate styes.

Prognosis and Treatment.—The disorder is primarily harmless, but the lesions if untreated are persistent and if secondarily infected are painful and dangerous. One should incise squeeze out the contents, and apply tincture of iodine to the cavities Fulguration is effective (Goodman BJD 47 413 1935) Sulfadiazine in a dose of 4 Gm per day will cure in a week or two Laymon (ADS 53 643 1946) reported in confirmation of Sommerville (BJD

53 255 1941) and this approach may be desirable when lesions are so numerous that surgical methods would be difficult Schiff (RhodeIMJ 30 806 1947) succeeded in a miliary case with sulfadiazine, and cures have been reported with oral Aureomycin (Guy et al. ADS 60 629 1949) and Terramycin (Mopper ADS 65 613 1952)

Eyelid margin cases with conjunctivitis can actually cause corneal ulceration (Gifford and Gifford AOphth 50 227 1921) They are best treated surgically (Julianelle and James AmJOphth 26 165 1943)

See Goodpasture and King (AmJPath 3: 385, 1927) cytology Goodpasture and Anderson (APath 30 12, 1940) immunity and chorioallantoic grafts Pinkus and Frisch (JID 11 280, 1949) skin test suggesting inflammatory reaction represents sensitization Blank (ActaD-V 29 92, 1949) histology, electron microscope studies of Boswell (JHExpPath 128: 351 1947), Rake and Blank (JID 15 81 1950 Melnick (Sc 114 484 1951) Mescon et al. (JID 23: 293, 1954) histochemical studies of inclusion bodies as they develop.

LYMPHOGRANULOMA VENEREUM

Symptoms.—Venereal lymphogranuloma is an infectious disease which is generally transmitted by sexual activity The first symptom is often a small ulceration a papule or a herpeslike lesion of the genitals The character of this primary lesion which often is unrecognized is variable Primary anorectal inoculation probably occurs (Grace and Henry NYSJM 40 285 1940) The incubation period is thought to range from 2 to 6 weeks from inoculation to lymph node enlargement The primary sore is often on the prepuce but adenitis may precede the appearance of a recognized primary A genital lesion may start to heal when the bubo develops but in the absence of bubo the ulcerations may be resistant (Brandt VDI 22 248 1941) In women the portal of entry may remain obscure The nodes which drain the portal of entry usually the inguinal nodes of one or both sides become swollen and tender and ultimately the overlying skin assumes a purplish hue and finally ulcerates. Multiple sinuses connect the suppurating nodes with the surface Healing is slow and cicatrices are thick and puckered Adenitis was bilateral in 21% of the cases of Prehn (ADS 35 231 1937) and it showed no predilection as to side Lymph nodes became suppurative in 75 of the cases The temperature averaged 100° F the highest noted was 106° F Slight anemia and slight mononucleosis characterized the blood picture Contact infection are possible Cases have involved the tongue and submaxillary glands Hellerström described infection of a physician's finger the axillary lymphatics underwent the usual course of venereal lymphogranuloma Extragenital lesions, including those of head and neck, were reviewed by Slaughter (SGO 24 390 1940)

Anorectal Lymphatics rather than the inguinal may be involved usually in women for anatomic reasons. The chronic inflammatory response and lymphatic obstruction lead to rectal stricture and perineal distortion even elephantiasis esthiomene This becomes a most stubborn and resistant condition The chronic ulcerative process involving the labia, perineum anus, and lower rectum may be of the superficial, perforating hypertrophic or mixed type Rectal strictures involve the female by preference (Cole J 101 1069 1933) and are located in the lower 10 cm of the bowel generally not higher than 6 cm They may be bandlike or tubular Stricture has been seen in male homosexuals. Some cases of ulcerative colitis are due to venereal lymphogranuloma Urethral anorectal and genital syndromes in women overlap Treatment of rectal stricture is largely by mechanical and surgical means, the requirement for which has not been supplanted by the limited benefits obtainable with antibiotics (Daniv SouthMJ 46 269 1953)

Constitutional Symptoms Exanthems and Complications —Along with local lymph node reaction one occasionally finds generalized lymph node enlargement The spleen may be enlarged Polyarthritis may be present Abdominal and pelvic inflammation have been shown due to lymphogranuloma

tosis in fatal cases. General skin manifestations, such as erythema nodosum erythema multiforme-like eruptions, urticaria scarlatiniform eruptions, and disseminated ulceration have been noted. When erythema nodosum occurs, it becomes manifest simultaneously with the development of cutaneous allergy and reaches its maximum when the inguinal adenitis is most intense (Heller





Fig. 252.—Esthiomene and perianal fist la, positive Frei test. (Crossen Diseases of Women, Mosby ed. 8 1953.)

Fig. 253.—Perianal scarring with rectal stricture. (Crossen Diseases of Women, Mosby ed. 8, 1953.)



Fig. 254.—Venereal lymphogranuloma penil lesion and lymphadenopathy Note two positive Frei test reactions on forearm. (Cole J 101 1049 1932.)

ström ActaMScand 109 1 1941) it may develop after interventions which alter the allergic status, such as the performance of the Frei test. A rash was elicited by exposure to sunshine in 60% of women with chronic disease a smaller proportion of acute cases and of cases in males, according to Sonck (abs ADS 54 216 1946) Erythematous papules and wheals were noted,

sometimes quite itchy affecting especially the extensor aspects of the extremities. Photosensitivity apparently occurs from 5 to 6 weeks after the lymphatic symptoms start and it disappears when the disease is cured

Ocular Lesions have been attributed to lymphogranuloma venereum (Macnie AOphth 25 255 1941) The infection can cause conjunctivitis, keratoconjunctivitis and uveitis (Espildora and Coutts AmJOphth 25 916 1942) Curth et al. (J 115 445 1940)

Parinaud's syndrome and keratoconjunctivitis have been proved to be of this nature (Schele et al. J 135 333 1947)

Genitourinary Manifestations may be primary with infection of meatus or urethritis. Later stricture of the urethra or perigenital sinuses and fistulae may develop Invasion of the posterior urethra and spread to prostate seminal vesicles and epididymis may take place Secondarily the bladder neck may be deformed displaced or compressed, and even the pelvic ureter may be forced to dilate (Coutts JUrol 49 595 1943) Urethral discharge with inguinal adenopathy calls for a Frei test for the primary sore of lymphopathia may be intraurethral just as the syphilitic chancre may be

Pregnancy and lymphogranuloma venereum rarely influence one another unless mechanical interference occurs (Wilson and Hesseltine AmJOG 43 459 1942)

Bone and Joint Manifestations are not common, but arthralgia acute polyarthritis, and chronic recurrent polyarthritis have been noted. In 2 of 4 such patients of Hickam (ADS 51 330 1945) pustular eruptions and fever followed Frei testing Osseous lesions were reviewed by Wright and Logan (ASurg 39 108 1939) they described instances of necrosis of the pubes possibly due to direct extension of the infection.

Neurologic Involvement was described by A Hamm and D Annov (J 106 1642 1936) whose patients had fever headache sweats, and painful stiffness of the neck. Active virus was obtained from the spinal fluid The spinal fluid showed enormous increase of total protein but responded to sulfonamide therapy in the cases of acute meningoencephalitis of Zarafonetis (NEngJM 230 567 1944)

In Children.—Ten nonvenereal cases in children 2 weeks to 14 years of age (Levy JPediat 11 812, 1937) and the case of an infant reported by Thompson and Higgins (AmJSyph 33 473 1949) show that the disease must be considered in the differential diagnosis of lymphadenopathy in young patients.

Etiology Pathology and Diagnosis.—The presence of venereal lymphogranuloma infection is often obfuscated by other venereal diseases. No especial racial susceptibility is discerned, although Negroes are often the victims. The disease is of world wide distribution most frequent in the Tropics (J 116 2405 1941)

In studying the venereal transmission of the disease and the high preponderance of male victims Bejarano and Calatayud (Crón. Méd. 1933, p. 771) found 11 4 of 75 apparently healthy prostitutes gave strongly positive Frei tests despite negative histories and examinations. Some observers believe that a woman may be a carrier of the disease without being a sufferer from it.

The inflammatory process may be acute subacute or chronic according to Hornbleth (BOH 63 90 1936) who determined that the histologic unit of the disease is an inflammatory nodule which undergoes necrosis. Primary lesions and lymph nodes in cases proved by isolation of the virus showed the same structure being granulomas composed of large mononuclear cells forming about the small vessels, which undergo compression and obliteration. This leads to necrosis in the center of the granuloma and abscess formation not due to thrombosis or endothelial proliferation and there is little fibrosis either in acute or healed lesions according to Sheldon and Heyman (AmJPath 23 653, 1947) See Favre (Annal) D 49 1940) photomicrographs of histology and granular corpuscles, silver staining

Serum Proteins are increased by the infection, sometimes before the Frei test becomes positive Serum protein exceeded 8 Gm./100 cc in 63 of 67 cases of Kampmeier et al (AmJMSc 198 610 1939) While this change is not specifically diagnostic it is significant, and hyperglobulinemia responds to sulfonamide treatment (Schamberg: AmJMedSci



Fig 255.—Lymphopathia venerea. (Dr O G Costa.)

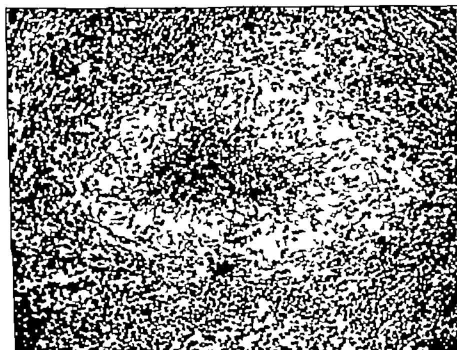


Fig. 256.—Venereal lymphogranuloma. Epithelioid nodule in a lymph node removed 2 months after onset of symptoms. Note invasion of the center by leukocytes and plasma cells, and absence of extensive necrosis. (Kornblith, [illegible] 43: 99, 193[illegible].)

201: 67 1941) The Formol gel test, indicative of hyperglobulinemia, affords reliable help in diagnosis and interpretation of response of the disease to treatment, according to Combes et al. (AmJSyph 29: 611 1945)

See Howard et al. (AmJSyph 22: 32, 1938) hyperproteinemia with reduction of albumin and increase of globulin reverts toward normal with healing of active lesions; Rosen et al. (ADS 39: 211 1939) hyperglobulinemia in 100% of 116 cases, most marked in rectal stricture, while serum lipids are decreased in lymphopathia venerea, not in chancroid.

COMPLEMENT FIXATION TESTS probably have significance (Beeson and Miller: AmJ PubH 34 1076, 1944; Wall et al. AmJSyph 31: 89 1947)

THE VIRUS.—Hellerström demonstrated the existence of a filtrable virus as the cause, and he transmitted the infection to animals. Miyagawa (JapJD 39 103 1936) reported the cultivation of the virus in the allantois of chick embryos. Beautiful illustrations of virus colonies developing in the epithelial cells of corneal cultures from puppy embryos were published by Malamos (ZtschrBakt 142: 1 1938); see Meixner (DWchn 106 325 1938) Coutts et al. (JTropM 43: 137 1943) Transmission of the virus to monkeys and the virucidal property of human serum from patients with the disease were described by Hellerström and Wassén (Epidemiology and Etiology of Lymphogranuloma Inguinale, Masson, 1934) Tamura (J 103: 409, 1934 JLabClinM 20: 393 1933) grew the virus in tissue culture in Tyrode medium and transmitted it thence to guinea pigs. The heated culture he found therapeutically useful. Wassén has inoculated human beings with virulent mouse brain antigen and obtained typical infection (Hellerström: ActaD-V 21 231 1940) The incubation period was from 15 to 24 days. Wilmoth (JTropM 39: 173, 1936) transmitted the disease to a human subject, using virus grown artificially

FREI TEST.—Frei (KlinWchn 4: 148, 1925; J 110: 1633, 1938) first demonstrated a specific skin reaction with sterile bubo pus. The reaction becomes positive within a few weeks after lymphadenitis appears. Frei test reactivity apparently remains positive during life once it has become positive. It is uniformly positive if the bubo has lasted 40 days. Mouse brain or chick yolk sac infections provide satisfactory antigens.

The Frei test is a small scale reproduction of the disease. The typical nodule comprises a shell of palisaded layers of epithelioid cells with a central granular core composed of the debris of leukocytes lymphocytes and endothelial cells. Plasma cells develop after the more acute phase. The spread of the process may lead to the formation of sinuses or abscesses; the involved nodes may coalesce or remain distinct. Sometimes there occurs spontaneous healing. Donovan bodies are not found in lymphogranuloma inguinale

Treatment.—Surgical removal of infected lymph nodes was at one time recommended but injections of Frei antigen and the use of sulfonamides and antibiotics are followed by better results. Fluctuant buboes should be aspirated (Kornblith AmJDigD 6 712, 1939)

Human antigen for therapeutic purposes was prepared by Hellerström (ActaD V 17 293 1936) from pus obtained by aspiration from a fresh bubo. This was diluted 1 to 8 filtered through paper and inactivated by 2 hours exposure to 60° C He added 0.5% phenol and gave doses of from 0.5 to 2.0 cc intravenously Wien and Perlstein (BJD 49 63 1937) thought the intradermal method of giving antigen in treatment seemed to hasten resolution. The intradermal route was preferred by Anderson and Harmos (Surg 3 41 1938) starting with 0.05 cc and increasing by that amount to a maximum of 1.0 cc. Vaccinal therapy with specific antigen is best accomplished by using subcutaneous injections in courses alternated with intravenous, allowing short rest periods after each of the latter Focal reactions and variable febrile and constitutional symptoms may be expected. Autogenous blood serum contains specific antigen and may be injected subcutaneously in treatment (Marks SouthMJ 35 1092 1942) Injections of the specific antigen may provoke undesirably severe systemic reactions and rashes.

Supportive measures should be maintained during courses of injections and rest periods. These include the urging of fluids, bed rest and light diet during the febrile stage of the disease aspirin medication and local heat applications for arthralgia and myalgia aspiration of fluctuant buboes enemas daily of 1:5000 potassium permanganate low residue diet, mineral oil and mild laxatives for anorectal cases iron medication for secondary anemia douches and the frequent application of 25% balsam of Peru ointment for vulvar and vaginal ulceration. Colostomy is likely to become necessary in rectal cases.

Mice infected experimentally can be saved by sulfanilamide a therapeutic response different from that of other virus diseases, excepting influenza (MacCallum and Findlay Lancet 2 136 1938) Sulfanilamide has been used in

human cases with good effect (Shaffer and Arnold ADS 38 705 1938) The dose must be large. Probably the best treatment available in 1948 comprised Frei vaccine intravenously on alternate days, sulfanilamide rest and artificial fever therapy in hospital (Costello and Cohen ADS 44 391 1941) After review of 388 cases at Bellevue Hospital, Costello and D Avanzo (ADS 57 112 1948) concluded that sulfonamides and bed rest were the best treatment in the early stage Fever therapy and sulfonamide were given together by Trautman and Thomason (NOrlM&SJ 92: 441 1940) with good results claimed. Sulfonamide was adjudged specific and was said to reverse the Frei test in many cases, by Stein (AmJSyph 24 454, 1940) After sulfathiazole has been given for 2 weeks, the virus can no longer be cultivated from the bubo (Heyman et al AmJSyph 31 81 1947) while in untreated cases chick embryo cultures remained positive for 3 months or more The dose should maintain a blood level of from 3.5 to 6 mg % and sulfadiazine and sulfamerazine were preferred by Rake (AmJTropM 28 555 1948)

Aureomycin has exhibited striking activity against many rickettsiae and certain viruses, and is highly effective in the treatment of mice infected intracerebrally with the virus of lymphogranuloma venereum Available to Wright et al. (J 138 408 1948) in vials for intramuscular injection, it was given to human cases in doses of from 10 to 40 mg per day In all cases so treated there was reduction of the size of buboes within 4 days, and the inclusion and elementary bodies showed degeneration and disappearance within 48 hours. Improvement and relief of pain in 4 days were observed in 40 cases treated with Aureomycin by Prigot et al. (NYSJM 49 1911 1949) although Robinson et al (AmJSyph 34 46 1950) expressed disappointment with this drug The late manifestations were helped more than the early ones by Aureomycin especially those with proctitis or stricture according to Wammock et al. (JID 14 427 1950) who recommended a dose of 0.5 Gm q.i.d to a total of from 20 to 30 Gm. Tetracycline is curative also (Maynard et al. AmJSyph 38 606 1954)

Terramycin proved highly effectual in West African males treated with 1 Gm. 4 times a day for 7 days by Henley (BritJVD 29 36 1953) and chloramphenicol is also effective according to Robinson (ADS 64 284, 1951)

Potassium antimony tartrate 5 cc of the 1% solution given twice a week may be beneficial in the early stages. Lithium antimony thiomalate (Anthiomaline) was recommended by Law (Lancet 1 300 1943)

Carcinoma of the female ano-genital region is an unusual concomitant probably merely coincidental, but one must be alert to the possibility so as to apply treatment which is appropriate (White and Miller AmJSyph 37 177 1953)

GENERAL REFERENCES.—Coutts (JTropM 37 97, 1934) Greeks and Romans knew the disease, which is also illustrated on Incan pottery; Sturber and Ploch (ADS 32, 86, 1935), penile and scrotal elephantiasis Thompson (J 104 1869 1935) general description De Wolf and Loring (J 106 1874, 1936) contact infection, encephalitis, oral lesions, D'Aunoy and Schenken (J 110 709 1938), pelvic inflammatory disease; Stokes et al. (AmJMedSci 197 878, 1939), review and bibliography Torpin et al. (AmJSurg 43: 688, 1939) 146 cases of which 96 affected females, grouped among 4 classes, genital, urethral, inguinal, anorectal, and sulfonamide therapy; Favre and Hellerström Rev d'Hyg 61, no 6-7, 1939) 87 pages, no pictures, extensive bibliography D'Aunoy and v Haam (APath 27 1032, 1939) review and bibliography Costello and Cohen (ADS 44 391 1941) 187 Bellevue cases, treatment with sulfonamide and Frei antigen Pund and Lacy (AmSurg 17 711, 1951) among cases of anogenital cancer a high proportion had positive Frei test, questionable etiologic relationship.

RECTAL STRICTURE.—DeWolf and VanCleve (J 99 1065, 1932) on rectal stricture Bloom (BGO 58 827 1934) on esthiomene and lymphatic anatomy Stillman (AnnSurg 101 1284 1935) stricture and colostomy VanderVeer et al. (AmJMedSci 190 178, 1935) 47 cases with 21 rectal strictures causing increasing constipation, pain, bleeding fecal incontinence, rectal discharge Wein et al (APath 10 121, 1935), autopsies on 3 Negro women Peyton (AmJSyph 24 360, 1940) types of stricture Grace (J 122 74 1943) anorectal cases Longmire (Surg 15 997 1944) pararectal abscess, fistula, rectal ulcer stricture, colostomy anemia from bleeding, hemorrhage, obstruction, perforation, acute belly from lymphopathia venerea.

EXANTHEMS.—Coutts (DWchn 87 1664, 1933) marginate glossitis sometimes with bullae, and cervical adenopathy Myerson (J 117 1077, 1941) pharyngeal and laryngeal lesion, Sezary (ADS 31 348, 1935) disseminated eruptions, nodular papular esteulopustule following x-ray therapy of primary or Frei testing Wein and Perlstein (J 109 27 1937), cutaneous ulcers Miescher (DZtschr 73 337, 1936) bulla; Meissner and Epps (DWchn 107 1466, 1930; AfDuS 176 100, 1938) morbilliform rash with fever e. multiforme and e.

nodosum with fe er anemia, cachexia; Costello and Cohen (ADS 41 557 1940) lymphadenitis neck and groin, recommending Frei test in any case of unexplained adenitis Simpson (ADS 66 526, 1952) metastatic bubo, neck and groin.

NEUROLOGIC INVOLVEMENT.—Gutman (NYSJM 39 1420 1939) myalgia, arthralgia and meningeal irritation Rubin and Aring (J 1?0 1276, 191) meningoencephalit case cured with sulfonamide, Laifer (ADS 55 899 1947) CSF normal in 2, etc Vinberg et al (JVDI 30 291 1949) of 82 cases, 19 show d CSF abnormality mainly with colloidal changes f protein content.

FREI TEST.—Grace and Suskind (ADS 34 65 1936) mouse brain antigen best for routine use, Strauss and Howard (J 106: 517 1936) mouse brain antigen unreliable Connor et L (JInfectD 60 62, 1937) Frei test latent period ranges from 5 t 39 days Hinkley et L (ADS 38 383 1938) human antigen preferred to mouse brain antigen Brandt nd Torpin (AmJSyph 24 632, 1940) interpretation of skin test Smith (ADS 41 128, 1940) histology of Fre test papule Rakin et al. (J 116: 2882, 1941) antigen from hick embryo yolk sac Lygranum, preferred to mouse brai antigen Robinson nd Robinson (ADS 45 11., 1942) interpretation Combes et al. (ADS 46: 264 1942) Lygranum qu te reliable, Curth (AmJSyph 27 47 1943) questionabl reliability Grace et L (ADS 65 248 1952) i hibition of positi e Frei reaction by cortisone

CAT SCRATCH DISEASE

This self limited infection presumably viral, is clinically suggestive of but milder than, tularemia. Seen more frequently in children than in adult It is characterized by subacute lymphadenitis which sometimes suppurates (Debré et al. SemHôp 26: 1805, 1950) This may be painful, is accompanied by mild fever and malaise and i usu ally preceded by a small maculovesicular kin lesion. A primary lesion, a scratch scar covered by a crusted erythematous papule at the site of inoculation may be found within



Fig. 25 —Cat scratch fe er Mal 36 years old, with cervical lymphadenitis and pink macula rash becoming vesicula on rms and forearms (G eer and Keefer NEngJM 244 545, 1951)

2 t 4 days The adult patient of Gree and Keefer (NEngJM 44: 545 1951) had a macular pinkish ra h which grad ally became vesicular and wa located on the extenso surfaces of th arms. Epstein (ADS 66: 40 195) described the skin lesions, the ecthymatous chancre and the rashes resembling erythema multiforme or erythema nodosum Systemic manifestations are slight and transient, wh le local manifestations comprise typicall) aden pathy which m y be huge with bubo formatio and drain g sinuses.

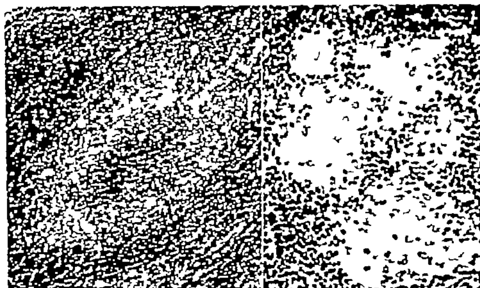
Suppuration took place in about one-third of the 60 American cases collected by Dan els and MacM rray (AnnIntM 37 697 195.) The bubo pus is bacteriologically sterile (Thelin and Martin du Pan: Praxis 40 74 1951) and leukocytosi i sually ab sent

Antigen analogous to the Frei antigen of lymphopathia venerea can be m de from bubo pus nd yields positive tuberculoid and/or erythemato skin tests (W ters et al.: Ped. 10 311 1952) The antigen tested in 40 cat owners who denied experiencing symptoms of the disease proved positive in 3, suggesting that the disease m y be specific a d inconspicuou t t mes (Battley and I rb rn Lancet 1 520 1953)

The disease has been known to occur in small epidemics (Lemaire and Debray: BullmemSocmédHôpParis 66: 375, 1950 see Edit.: J 149 746 1952) Cases have been reported by Tonge et al. (MJAustral 81 1953) from Queensla d, and by Thompson and Miller (AnnIntM 39 146, 1953) whose e cephal ti pat nt contracted the disease b dressing rabb ts. Twelve cases from South Tex w re reported b Daeschner et al (JPediat 43: 371 1953) The infect on a sed the death f th patient of Gräff (Monatsch Kinderh 102 23., 1954)

While the history of exposure to cats is usually clear the disease m y occur following exposure to other a imals (Bennett and Melton: JMAGa 40: 466, 1951) Sniffi g cat uri e apparently resulted in throat inoculation with cervical adenopathy in a case of Daniels and MacMurray (AIntM 88: 720 1951)

The possible relation to Parinaud s oculoglandular syndrome was discussed by van Veelan and Stibbe (abs J 153 453, 1953), whose patient manifested conjunctivitis edema of the lids, swelling of the left ear and jaw and regional lymph node enlargement in 1948 and gave a positive reaction to cat scratch antigen in 195_. This idea had occurred to de Lavergne et al. (BullmémSocMHôp 67: 953, 1951) and was promoted also by Cassady and Culbertson (AOphth 50: 68, 1953); see Edit. (J 152: 1717 1953) The uveoparotid syndrome of Heerfordt (AfOphth 0 _54, 1909) might be of this nature; a case with headache, iridocyclitis, f cial palsy parotid swelling, and high total protein in the spinal fluid, as in infectious neuronitis was described by Tepper (BMJ _ 1954, 194)



Figs 248 and 249—Cat scratch disease, histopathology of the enlarged lymph nodes. (W ters and Prior: Pediat 10: 211 1952)

Histologic st dies by Molla et t al. (PresseMéd 58: 1353, 1950) revealed in the lymph nodes reticular hyperplasia which might remain stationary or regress, but which often progressed to the formation of ecrotic foci microscopic abscesses, suppuration and periadenitis. Basophile bodies were fou d in the cytoplasm of the lymphocytes, plasma cells and reticulocytes stai ed by Giemsa s method and were attributed to the presence of a virus by Mollaret et al. (PresseMéd 59 681, 701, 1951) Their presence was con firmed by Jambor and Emura (ADS 67 439 1953) who noted the histologic similarity to lymphopathia venerea of this benign inoculation lymphoreticulosis.

Treatment is as yet nonspecific.

Para-anthrax, allegedly due to *B anthracoides* manifests accompanying lymphadenitis. It followed a cat scratch in the case of Epstein (ADS 57: 664, 1948) and was not responsive to penicillin o sulfonamides.

DERMATOSES DUE TO RICKETTSIAE

Rickettsiae, like viruses, are obligate intracellular parasites. They are, for the most part, microscopically visible gram negative, bacteria like bodies found in the alimentary canals of arthropods and frequently associated with disease in man and animals. Electron microscopy shows cell walls and nuclei and rickettsiae behave immunologically like viruses and bacteria (Mudd: J 126 561 632, 1944) See Rivers et al. (Viral and Rickettsial Infections of Man Lippincott, 1952)

The diseases of man with which species of Rickettsia are associated and of which the epidemiologic character is determined by the life cycles and the feeding habits of the arthropod vectors may be divided into four subdivisions: typhus, Rocky Mountain spotted fever tsutsugamushi and Q fever according to Dyer (J 124: 1165, 1944) whose résumé I quote here extensively The organisms of Q fever which is not associated with dermatologic symptoms, pass bacterial filters which retain other pathogenic rickettsiae.

A characteristic of this group of diseases with the exception of Q fever is the production in patients of agglutinins for the X strains of *B proteus*. Serums from typhus and spotted fever agglutinate the OX_{19} and OX_2 strain while those from tsutsugamushi agglutinate the OXK strain, typically but no strain of *B proteus* has been found which is agglutinated by serums from Q fever The absence of cross immunity also separates subdivisions of rickettsial infections.

Clinically the typhus, spotted fever and tsutsugamushi groups are characterized by sudden onset, rash, fever of fairly well-defined duration mental disturbance and pronounced prostration. Epidemic (louse-borne) and endemic (murine or flea borne) types of the typhus subdivision are recognized. The Rocky Mountain spotted fever subdivision not so clearly delineated but includes other or similar tick borne diseases, such a boutonneuse fever the misnamed São Paulo exanthematic typhus, the so-called tick typhus of India, and South African tick bite fever The tsutsugamushi subdivision embraces also scrub typhus and other mite born diseases of southern Asia and the Southwest Pacific Islands.

Pathologically characteristic changes consisting of vasculitis and perivasculitis are caused by rickettsiae, which, if carefully sought, can usually be found in the endothelial cells lining the blood vessels, especially the smaller ones of the brain, lungs, heart, and skin (Mandelbaum and Hollander: AmM 3: 316, 1947) A skin biopsy selecting a well developed lesion of the macular type is excised sharp fixed in Regaud's fluid, and stained by the Giemsa method. Rickettsiae can usually be found, but if they are not, the proliferative endangiitis is diagnostic The similarities of thromboangiitis obliterans and rickettsial damage to endothelium led Goodman (ASurg 35: 1176 1937) to hypothesize a relationship.

Viable rickettsiae were isolated from a lymph node excised a year after clinical cure of a patient with Rocky Mt. spotted fever by Parker et al. (JImmunol 73 383 1954)

See Weil and Felix (WienKlinWchn 29 33, 1916) serodiagnosis. Hertig and Wolbach (JMRes 44 329 1924), rickettsiae in insects, tabulation and demonstration Cox (Sci 94 399 1941) yolk sac culture, skin test and vaccine Davis (PHRpts 58 1201, 1943), transmission of spotted fevers by *Ornithodorus parkeri*. Castaneda (... J 121 ... 1933) staining of rickettsiae thin smear dry well xylene 3 min ... wash twice with 95% alcohol then with water cover for 3 minutes with saturated solution potassium bichromate wash with water cover with 10% Giemsa solution for 10-20 minutes wash with water dry and examine rickettsiae red or blue on almost colorless background, clearly differentiated. Parker (J 110 1185 1273 1938) valuable résumé of rickettsioses, particularly Rocky Mt spotted fever

Epidemic Typhus.—The body louse and the head louse which are probably not different species, carry typhus (*R prowazeki*) from one human being to another The infection kills the louse within 12 days (Parker J 110 1185 1273 1938) The incubation period is from 5 to 15 days usually 8 to 12 days. Onset may be preceded by a day or two of malaise but the majority of cases show abrupt onset with rapidly rising fever repeated but seldom severe chills and headache. Fever rises steadily reaching a maximum by the end of the first week with slight morning recessions Fever falls by rapid lysis after about 14 days. Headache is a prominent symptom hard to relieve Prostration and cardiac weakness may be evident from the start In severe cases with cardiac weakness there is a tendency toward development of gangrene of the extremities. Confusion disorientation, restlessness, irritability even delirium occur

A characteristic feature of the disease is the rash, which appears about the fourth to sixth day perhaps as early as the third day or as late as the

ninth. The rash is absent in about 10% of the cases, and may be hard to see on pigmented skins (Megaw BMJ 2 401 1942). Conjunctival red spots are an almost constant finding and may be the only distinguishing feature on gross inspection of the body of a person dying of typhus (Avtsin APath 36 158 1943). Rose red macules and papules, at first erythematous but later purpuric increase in number and extend for perhaps 48 hours their profusion being related to the severity of the disease. They occur first on the inner surfaces of the upper arms or on the sides of the chest and upper abdomen then spread to the rest of the chest trunk and extremities, even including palms and soles, but seldom affecting the neck and face. The rash becomes brownish as recovery ensues and eventually disappears. The fatality rate ranges from 20 to 80% in different epidemics.

Endemic (Murine) Typhus, differing from epidemic in epidemiology is due to *R. mooseri* and cases have occurred in every state of the United States. There is a reservoir of infection in the common rat and possibly in other rodents, transmission from rat to rat probably being accomplished by rat fleas and lice. Transmission to man probably is accomplished by infected feces of rat fleas. Clinical manifestations differ from those of epidemic typhus mainly in being milder. The rash seldom appears before the fifth day and may comprise only a few macules which soon disappear. Pink maculopapules becoming bluish red and slaty were described by Donald and Barker (BMJ 2 333 1942) appearing first on the shoulders about the axillary folds, then the upper abdomen and flanks, later on trunk and limbs, and prominently on forearms and dorsa of hands and feet. Fading is succeeded by mottling which may last for a month, with fine branny desquamation. The virus is endemic in various rodents many varieties of which are susceptible to infection (Brigham and Dyer J 110 180 1938).

A preventive vaccine from infected fleas was prepared but not highly praised by Dyer et al. (PHRpts 47 1329 1932).

In treatment para aminobenzoic acid in doses of 2 Gm each 2 hours until the temperature became normal was recommended by Smith (J 131 1114 1946) and the usefulness of this drug was further attested by Levy and Arnold (TexasSJM 42 314 1946). Chloromycetin in full oral dosage was curative in a case of McCrary (ArkMSJ 46 81 1949) and Ley et al. (J 143 217 1950) adjudged the drug promptly effectual. Achromycin was curative in cases of exanthematic typhus treated by Ruiz Sanchez et al. (Antibiot& Chemother 4 402, 1954).

Brill's Disease: see Murray et al. (J 142 1059 1950) rash 4th to 6th day, faint pink, discrete macules or maculopapules 1 to 10 mm diameter usually on front of chest extending rapidly over trunk and proximal parts of extremities, maximum by 7th or 8th day; very scanty in some cases.

Rocky Mountain Spotted Fever is found chiefly in the northwestern states of the Union, prevalent in sheep-herding districts. The disease in man has occurred in most of the 48 states. It affects especially outdoor people in the spring and early summer in the West, later in summer in higher altitudes. In any locale the mortality rate is about constant. In the Bitterroot Valley region of western Montana the rate in adults was near 80%, in infants 35%. In the East it ran about 25% before antibiotics were available.

The attack may be abortive, fulminating or of any degree of severity in between. In ambulatory cases the fever is low, the rash scanty and the duration only 14 days. A temperature of 104° F with fleeting rash and recovery in a week, characterizes the abortive case. Fulminating infections kill in 3 to 5 days with or without a rash which may be blotchy and ecchymotic. The incubation period of severe cases is 2 to 5 days and is prolonged to 3 to 14 days in milder cases. There may be a 2- or 3-day period of prodromal malaise, or the onset may be sudden. It is marked by chill, headache, pain in the upper abdomen, and pains in bones and muscles. The main complaints are frontal and occipital headache, low back pain and malaise. The rash depends patho-



Fig. 260.—Typhus, showing petechial rash. (Courtesy of Dr. J. J. Todd, from Moseby's Practice of Medicine. The C. V. Mosby Co.)

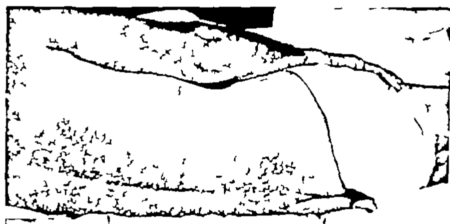


Fig. 261.—Rocky Mountain spotted fever. (Dr. J. J. Sippy.)

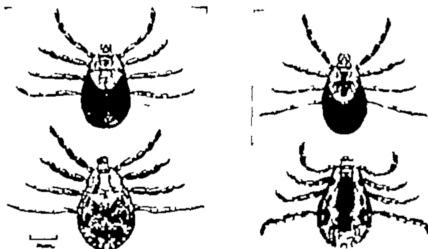


Fig. 262.—*Dermacentor andersoni*, female above, male below. (Dr. F. C. Bishopp, U. S. Dept. Agriculture, Bureau of Entomology and Plant Quarantine.)

Fig. 263.—*Dermacentor variabilis*, female above, male below. (Dr. F. C. Bishopp.)

logically on endangiitis of peripheral vessels. It appears on the second third, or fourth day rarely a day or two later It is first seen on the wrists and ankles, and spreads rapidly to the back, then to the arms, legs and chest and last to the abdomen Palms and soles are frequently involved often the face and occasionally even the scalp First pale and simulating the early rash of measles, the exanthem becomes bright rose in color and maculopapular It soon becomes purpuric and bluish Large sparsely distributed bright spots are of better prognostic import than small ones tending to become confluent.



Fig. 264.—Rocky Mountain spotted fever (Kelsey and Harrell J 137 1356, 1948)

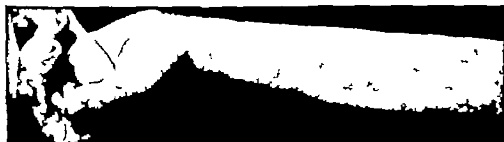


Fig. 265.—Rocky Mountain spotted fever (Drs. W M. Kelsey and G. T Harrell.)

The rash comes in crops, of which there may be one, two or three Sloughs due to endothelial necrosis may involve the scrotum prepuce, vulva, buttocks, or palate (Pullen et al. NOrlM&SJ 97 359 1945) The fever persists for 2 or 3 weeks, and the eruption clears as bruises do if the patient recovers. Desquamation occurs at the end of the third or fourth week (Hutton J 117: 413 1941) The mortality throughout the United States in over 4 000 cases reported 1930 to 1946 averaged 23% (Edit : J 142 1217 1950)

See Ong and Raffetto (JPediat 17 647 1940), 18 cases District of Columbia region Ha ... et al (PaMJ 44 176 1940) 13 cases near Philadelphia Elsmore (OklaSMAJ 36 232, 1943) 7 cases in Oklahoma, tick host thought to be gopher; Smith and Reinhard (JMoMA 40: 166, 1943) and Casford (ib p. 171) Missouri cases Evans et al. (OhioSMJ 43 606,—1947) 70 cases i Ohio with 19 deaths.

ETIOLOGY.—*Dermacentor andersoni*, *D. variabilis* (dog tick) and *Haemaphysalis leporis-palustris* (rabbit tick) can carry *R. rickettsi* which causes spotted fever; other ticks have been proved capable of carrying it. The virus is not transmitted until the tick has been feeding for 8 to 24 hours. The patient of Bauersfeld (J 11?: 1319 1939) was infected by removing a tick from her husband and she died.

PROPHYLAXIS AND CONTROL.—One should wear boots, leggings and puttees and hunt for and remove ticks twice a day; the search must miss no area of the body. All clothing should be removed at night. Persons should sleep separately. The clothes must be kept off the ground. In choosing a camp site select timber country and scant vegetation. Avoid rodents, sagebrush, and old trails. One should avoid infected areas. Dibutyl phthalate rubbed into the clothing gives protection and withstands several launderings of the garments (Council Rpt. BMJ 2: 87 1946).

If specific immune serum is injected into the site of a bite of an infected tick within 48 hours, protection against disease and yet development of active immunity ensued in experimental animals (Edit. J 125: 11 1944). The practical value of this interception of infection has not as yet been determined.

VACCINE is prepared by grinding infected ticks to make a phenolized emulsion; after settling the supernatant fluid is used. It is given in two subcutaneous injections of 2 cc each for adults and 1 cc each for children under 10 years; 3 injections may be given instead of 2. Children are better protected than adults. The vaccination must be repeated annually in the spring and it will protect for the remainder of the year. See Cox (Sci 94: 399 1941), Parker (AmJTropM 21 369 1941). The rickettsiae were cultivated in the chick chorioallantois by Bengtson and Dyer (PHRpts 50 1489 1935). A vaccine prepared from a saline suspension of infected chick embryo membranes, inactivated by formaldehyde and extracted with ether to remove yolk lipids and tissue debris, contains the immunizing antigens (Craigie, CanadJRes 23: 104 1945; see J 139 839 1948). It appears to have value in preventing Rocky Mt. spotted fever (Squibb makes it). Vaccine made from chick embryo cultures entail the hazard of an egg protein content and skin testing should precede its use (Ratner and Untracht: J 132: 899 1946).

TREATMENT.—Rest, hospital care and symptomatic and supportive treatment are required in cases which are not mild. Pointing to the loss of protein and low serum levels which develop Harrell et al. (SouthMJ 39 551 1946) urged a high protein diet because the antiserum, admittedly valuable if given before the third day, does not prevent protein depletion. A high protein, high-calorie diet decreased wastage of nitrogen and loss of body weight in patients of Tierney and Yeomans (JClinInv 25 822 1946) who found depression of the albumin fraction and striking elevation of the globulin fraction in the serums of most cases.

Chloromycetin inhibits various viruses, rickettsiae and bacteria, protecting chick embryos and mice from infection (Ehrlich et al. Sc 106 417 1947). Effective when given orally, doses of 1.0 Gm. initially followed by 0.2 Gm each 4 hours cured typhus in human beings (Smadel et al. cited J 138 432, 1948. BMJ 2 428 1948). It is dramatically beneficial in scrub typhus. Improvement was steady following the first dose and the eruption did not spread, and there were no deaths among the patients treated with Chloromycetin by Pincoffs et al. (AnnIntM 29 656 1948). The drug cured cases of epidemic typhus for Benhamou et al. (PresseMéd 58 317 1950). Symptoms receded after 24 hours and fever lasted only 4 days in 16 patients treated with Chloromycetin by Parker et al. (AmJMed 9 308 1950). Cortisone combined with the antibiotic seemed advantageous to Workman et al. (NEngJM 246 962, 1952).

Aureomycin was effective and preferable to PABA in the experience of Ross et al. (J 138 1213 1948). See Cooke (J 138 885 1948). Terramycin likewise gave striking abatement of symptoms within 48 hours (Powell et al. BullJHH 89 10 1951).

In managing gangrene, which is dry and affects particularly the lower extremities, sometimes costing one or more toes, one waits for demarcation before undertaking surgery (Constantini et al. PresseMéd 46 75 1938).

Topping's antispotted fever rabbit serum may be dramatic if given early in a dose of 1 cc. per kg. according to Meade (VaMMonth 73 16 1946). Para-aminobenzoic acid given in large doses is of real utility (Rose et al. J 129 1160 1945; Flinn et al. J 132 911, 1946; Tierney SouthMJ 40 81 1947; Ravenel ib 40: 801 1947). The dose is 6 to 8 Gm. initially, then 2 or 3 Gm. each 2 hours. To be effective it is to be started before the end of the first week. The blood concentration should be kept around 30 to 40 mg. %

The drug must be stopped if the white blood cell count becomes less than 3,000. Methylthionine chloride, 0.5% added to the diet of experimentally infected mice was more effective than PABA (McClymans and Grant: Sc 105: 181 1947)

Treatment of a comprehensive sort includes restoration of fluid and electrolyte balance by intravenous dextrose in saline or lactate-Ringer's solution, correction of acidosis by one-sixth molar sodium lactate, correction of serum protein depletion by intravenous plasma, provision of high vitamin intake, administration of PABA with alertness to its possible intolerance, and attention to possible complications such as congestive heart failure, pneumonia, and thrombophlebitis (Ravenel: J 133: 989 1947)

Neoarsphenamine dissolved in aqueous Metaphen was recommended by Reich (An IntM 17: 47 194)

See Topping (PHRpts 58 757 1943): immune serum in experimental infections of guinea pigs and monkeys suppressed disease if given early, ameliorated if given within 72 hours. Yeomans et al. (J 129 19 1945): amelioration in human cases; Tierney et al. (JPed 31 1 1947): no deaths in 8 cases treated with PABA; Fraser et al. (AmJDisChild 75 492, 1948): odd seizures by giving sodium salt of PABA; Woodward and Raby (SouthMJ 41 997 1948): blood level 40 mg. lessened fever rapidly, no relapse on discontinuing PABA after temperature became normal; Kelsey and Harrell (J 137 1356 1948): PABA helped, rabbit serum seemed not helpful; Hooten et al. (VMMonth 8 121 1949): PABA the drug of choice at that time.

Rat-Mite Dermatitis.—Dove and Shelmire (J 96: 579 1931 97: 1506 1931) described an acariasis in northern Texas due to the blood-sucking rat mite *Liponyssus bacoti* Hirst. These mites can convey endemic typhus, or Brill's disease. If they are infected, a febrile course follows their bites and persists for about two weeks.

Tick-Bite Fever.—South African tick-bite fever is due to rickettsial infection. It closely resembles fièvre boutonneuse, kedani and tsutsugamushi. In the region of Lorenzo Marques, no newcomer escapes this mild disease which is without mortality. In certain areas infected larval ticks, *Amblyomma hebraeum* are numerous in the tall grass. Their bites result in a pathognomonic initial sore, a raised, bright red, circular indurated lesion of ... cm. diameter with a necrotic black center. Rarely the primary sores are multiple. Two types of cases are distinguished, a mild type consisting merely of primary sore and satellite adenitis, and a severe type with the sore, adenitis, headache, rash, and fever of 10 days' duration with aching pains, photophobia, tremors and even delirium. The rash is not characteristic. It appears about the fifth day, being macular or papular, rosy or blotchy, diffuse or discrete, confined to the trunk, or generally distributed, including the palms and soles. A bright red papular type of rash is common, and it comes out in daily crops. Though not itchy it is somewhat uncomfortable. General symptoms include a step-up fever, severe headache, stiff neck, aching and restlessness. The fever drops on the tenth day. There are never sequelae, complications, or recurrences. The bubo does not suppurate. Immunity is solid following the infection. The serum agglutinates Proteus OX_{19} and OX, but not X Kingsbury (Pijper and Dau: BritJExpPath 1 ... 123, 1931). Infection of ... was achieved by Pijper and Dau (BritJExperPath 9 ...7 1930), who demonstrated rickettsiae in the brains of the animals (JTropM 33 93, 1930). See Troup and Pijper (Lancet ... 1183 1931); Pijper (SoAf MJ 8: 551, 1934); Pijper and Crocker (SoAf MJ 1... 613, 1938)

Aureomycin is successful in treatment, prior to the use of which PABA had been known to yield benefit that was not striking (Gear and Harrington: SoAf MJ 23 507, 1949). Fever drops and malaise dissipates within 72 hours after Aureomycin is started (Henderson et al. EAfrMJ ..: 140 1950)

Boutonneuse (Marseilles Fever) caused by *R. conori*, is closely related to Rocky Mt. spotted fever and may be identical with Kenya typhus. Infection is transmitted by the brown dog tick. The incubation period is 5 to 7 days, rarely as long as 18 days, and the onset is usually abrupt with fever and repeated chills, headache and muscle pains, but comparatively slight prostration. A papular or maculopapular rash appears on the second to fourth day of illness, starting on the trunk, legs and arms, and extending rapidly over the entire body, usually appearing last on the face. Volar skin is commonly involved. The soft palate may manifest small round red spots for only a few days. The lesions, especially in dependent locations, may become petechial but seldom coalesce. A small ulcer presumably indicating the site of the infecting tick bite, may be found early in the disease. It is only ... to 5 mm. in diameter showing a black necrotic center surrounded by a red areola. Chloromycetin is curative (Janbon et al.: PresseMéd 57 10.. 1949)

Tsutsugamushi (Japanese River Fever, Kedani Fever, Scrub Typhus) resembles the other rickettsial infections but is caused by *R. ... pyogenes*. It is probably identical with Malayan scrub typhus, Queensland coastal fever and pseudotyphus of Sumatra. The larval forms of certain mites transmit infection to man from reservoir probably in field mice and other rodents. The incubation period is from 7 to 21 days, generally a little less than two weeks. Prodromal symptoms occur as in typhus, and chilliness, headache and fever characterize the onset. Deafness is not a rare early symptom, and joint pains and drowsiness are often present. Fever with peaks produces considerable prostration, lasts about ... weeks and falls to normal. The striking feature of the patient's general appearance is apathy (Mc...h...lin and Forrester: AmJMSc ..10 33 1945). Fatalities occur in a range of from 1 to 10% in various epidemics (Brumpt: Précis de Parasitologie). Death occurs in coma between the 9th and 15th days.

The most characteristic sign is a small necrotic ulcer such as occurs in bouton euse, a d this is present in the majority of cases in Japan. It is not always found, however in cases called scrub typhus in Malaya. General lymphadenopathy develops and is especiall noticeable in nodes draining the site of the primary ulcer which usually occurs in the *pubic region axilla, or leg. The typical ra h of tsutsugamushi appears on the fourth to* eighth day and consists of macules and slightly elevated rose-red or pink papules. It does not become petechial. It appears first on the trunk and face and extends to the legs and arms. It may be present on the palms and soles, and occasionally the face a d the scalp are involved. The rash reaches its height i about 4 days a d fades within 6 or 7 days. An enanthem may be present on the soft palate. Conjunctivitis and mild edema of the *lids are usual (Ahlm and Lipshutz: J L.A 1095 1044)* Many patients show *bronchial* symptoms, sometimes with mucopurulent sputum, and pneumonia may occur as a complication. Hyperesthesia, pains in muscles and joints, deaf ess, apathy clouded mentality insomnia and delirium may be encountered (Dyer: J I 4 1164 1944)





Fig. 266.—Tick bite fever initial sore on cheek. (Dr A. Pijper)

Fig. 267.—Larva of *Rhipicephalus appendiculatus* the common vector of tick bit fever in South Africa. (Dr A. Pijper)



Fig 268 – Rash resembling that of typhus, seen in South African tick bite fev r (Dr A. Pijper)

Some mm nity is co ferred b an attack l t this may lack permanence. Cross immunity complete between rural typhus n Malaya a d tsutsugamushi in the guinea pig rabb t and monkey (Lewthwaite and Savoo : Br.J.Exper.Path 1: 448 461 1936) but this is not true f bu t phus, which f rthermore does not m nifest a primary sore Rocky Mt spotted fe v ine does not protect against ither rbe rural typhus.

Th path logy t th disease was especially st died l y Park and Hart (Am.J.Clin.Path 10 139 1940) wh found th most ignifi a t cha ges in the heart l g l mph odes, testes an l bra n The essential lesion are *disseminated perivascul tis nd focal i* terstitial, monoc t cel lar i filtrat sociated with edema and passive hyperemia, but the thrombot c lesio common in othe rickettsioses are extremely rare

Para-aminobenzoic acid, given so as to maintain 30 to 60 mg % concentration in the blood, apparently reduces symptoms, morbidity and mortality (Tierney: J 131: [illegible]40 1946). Methylene blue appears more effective than PABA, especially in the late stages (Edit.: BMJ 1: 403, 1947). Chloromycetin brings about improvement within a matter of hours, fever persisting on the average less than 30 hours after the drug is started, and is equally effective whether given early or late in the course of the disease (Smadel et al. JCI [illegible] 1196 1949). Infection may be prevented by rubbing dibutyl phthalate into the clothing as a repellent (see BMJ 2: 8 1940).

Trench Fever, also known as five-day fever or Volhynia fever, is transmitted to man by the body louse. This disease disappeared after World War I. The incubation period was from 5 to [illegible]0 days; onset was sudden with headache and pain in the legs and fever lasted about a week but frequently relapsed two or three times. A rash was present in the majority of cases, usually macular, sometimes papular, and was most commonly observed on the trunk. It sometimes disappeared in [illegible]4 hours. The disease was not fatal. It was controllable by installation of body lice.

RICKETTSIALPOX

Symptoms.—An initial lesion and a vesiculopapular type of eruption dermatologically characterize this interesting disorder which was recognized in an outbreak of previously unclassified disease which occurred in a Regency Park housing development in New York City in the summer of 1946. The initial lesion started as a papule, rounded and firm, enlarging and undergoing central, deeply seated vesiculation. The fluid was clear at first but became cloudy and the lesion shrank and dried so that a black eschar resulted. About one week after the start of the initial sore occurred the abrupt onset of chills, fever, sweats, frontal headache, and backache, coinciding with the height of development of the asymptomatic sore which attained a diameter of 5 to 20 mm., with surrounding erythema but no induration. Regional lymph nodes were usually enlarged and slightly tender. The sore persisted for a total of approximately 3 weeks and usually left a small scar. The sore may not have been noted by the patient.

The onset of illness was sudden, with fever low at first but rising rapidly to 103° to 104° F., with morning remissions for about a week, defervescing gradually. Chills occurred in 70% of the cases during the first 2 days and were followed by drenching sweats. Headache was usual and severe, and backache and myalgia resembled those of influenza. Lassitude was always present, photophobia sometimes and, less frequently, anorexia, dryness of the throat and nausea.

A rash appeared in all cases, usually being noted at the onset of fever or within a day or two later. The lesions were maculopapular, discrete and erythematous, the papules roughly circular, firm, and sometimes surrounded by erythema. They ranged from 2 to 8 mm. in diameter and underwent summit vesiculation simulating varicella within a day or two. The vesicles dried, a black crust formed, and healing occurred without scarring. The rash was scanty, moderate or abundant, and was without a pattern, though the volar skin was spared, and it endured usually for from 4 to 7 days. There were no physical signs of systemic disease other than those associated with fever. There was no fatality. Moderate leukopenia with occasional relative lymphocytosis was observed. The histopathology of the cutaneous lesions was described by Hersherberger and Huebner (PHRpts 62 1740 1947).

Etiology.—The mouse mite *Allodermanyssus sanguineus Hirst*, inhabiting the domicile of infected persons, was proved to carry the rickettsia, *R. akari*, which was shown to be the cause of the disease (Huebner et al. PHRpts 61 1605 1946; 62 777 1947). The house mouse was the probable carrier of the vector. The organism was grown in the yolk sacs of fertile eggs and produced illness in mice and guinea pigs. A yolk sac antigen gave specific complement fixation tests with human convalescent serum. Agglutinations with *B. proteus* OX_{19}, OX_2, and OXK were negative. An interesting account of the finding of the mites by Pomerantz, an exterminator, and Shankman, a physician, is given by Roueché (The New Yorker, Aug 30 1947 p 28). See Sulzberger et al (ADS 57 767 1948).





Fig. 269.—Rickettsialpox, initial lesion in fourth interspace. (Dr. Morris Greenberg, New York City Department of Health; J 133 901 1947.)

Fig. 270.—Rickettsialpox, initial lesion on leg. (Dr. A. C. LaBoccetta, Medical Director Philadelphia General Hospital. Am J Med 13 413, 1952.)



Fig. 271.—Rickettsialpox, varicelliform rash. (Dr. A. C. LaBoccetta.)



Fig. 272.—Rickettsialpox, vesicular and crusted lesions of face and tongue. (Dr. Morris Greenberg, New York City Department of Health.)

Treatment has been symptomatic, but aureomycin in full dosage by mouth restored the temperature to normal in 24 hours and relieved malaise in 5 cases, while untreated the disease could be expected to cause fever and symptoms for a week or more (Rose et al. AmJMed 9: 300, 1950).

See Rose (NYSJM 48: 2266, 1948) more than 350 cases on record; Greenberg et al. (PHRpts 64: 1677, 1949; J 133: 901, 1947; AmJPubH 37: 860, 1947) complete description; Rose (AnnIntM 31: 871, 1949) clinical; Barker (J 141: 1119, 1949) 12 cases; Pike et al. (NEngJM 242: 913, 1950) case in Bostonian; Franklin et al. (NEngJM 244: 509, 1951) case in Bostonian; LaBoccetta et al. (AmJMed 13: 412, 1952) Philadelphia cases.

An Undescribed Fever Resembling Rickettsialpox and Varicella was reported by Loewenthal (SoAfrMJ 24: 268, 1950) on the basis of 11 cases seen in children in the Transvaal. Malaise of from 3 to 4 days duration preceded the eruption, which was varicelliform, morbilliform, or papular. This appeared first on the oral mucosae, was full-blown in from 24 to 48 hours, and regressed in 8 days. An early symptom was asymmetric enlargement of the occipital and cervical lymph nodes. The disease was self limited and nonfatal.

DERMATOSES DUE TO BACTERIA

STAPHYLOCOCCIC INFECTIONS

Staphylococci are often pathogenic (see Blair BactRev 3 97, 1939) In the skin they can produce (1) epidermal infections such as impetigo (2) intracutaneous and follicular infections such as infectious eczematoid dermatitis and furuncles, and (3) deep infections such as carbuncle cellulitis, erysipelas-like lesions, abscesses and gangrene See Pillsbury (J 132 602, 1946) See Granuloma pyogenicum and Botryomycosis.

Breed et al. (Bergey Manual of Determinative Bacteriology Williams & Wilkins 1948, p. 235) combined the genera *Micrococcus* and *Staphylococcus* and described species of especial dermatologic interest among those which produce nitrites from nitrates but do not utilize $NH_4H_2PO_4$ as the sole source of nitrogen: *Micrococcus (Staphylococcus) pyogenes* var *aureus* liquefies gelatin ferments mannitol and produces abundant orange growth on agar media; *Micrococcus pyogenes* var *albus* differs only in manifesting white growth; and *Micrococcus citreus* manifests yellow growth. *Micrococcus epidermidis* liquefies gelatin very slowly or not at all, does not ferment mannitol and manifests a scant white translucent growth on agar media. These four species are aerobic to facultative anaerobic and do not produce pink or red pigment on agar media.

Staphylococcus pyogenes i the name that Bigger (BMJ : 837 1937) preferred for strains which hitherto have been known as *Staph. pyogenes aureus* and *Staph pyogenes albus* and he did not accept *Staph citreus* as a distinct species It was once thought that the activity of the staphylococcus is due solely to endotoxin but it was shown that a broth filtrate conta ns toxin capable of killing rabbits when given intravenously Necrosis is produced by the subcutaneous injection of the toxin. Hemolysin was demonstrated and its presence in filtrates was recognized in 1901 leukocidin was also discovered early Burnet (1929) studying the cause of death from injections of contaminated diphtheria antitoxin, described the intravenous toxicity dermonecrotic effect and hemolytic action of the exotoxin. Panton et al, discovered that intracutaneous injections of the exotoxin are immunizing Pathogenicity B gger noted is usually associated with the ability of the strain to produce pigment. Defense consists in elimination by leukocytes or prevention of toxic effects by antitoxins. The necrotizing substance causes obstruction to the local lymph flow and so plays an important part in determining the histologic and physiologic aspects of the inflammatory lesion

Staphylococcus toxin was the subject of an illuminating review by Rigdon (AmJMSc 199 41., 1940) There appears to be no relat onship between the quantity of toxin produced nd the irulence of the organism for man. The production of toxin by a given train is not constant. Fractions described include leukocidin, hemolysin, acute killing fraction, dermonecrotizing fraction neph otoxin, coagulase and fibrinolysin. It has not been proved whether these fractions are the same o different substances. The antigenic ty of co jugates of staph lococcus toxin w th other substances, a noted on p. 1°6, phe ome n of unassessed l ut perhaps great clinical sign fica ce The production of coagulase i strongly nd cative of pathogenicity (Moss AmJClinPath 11 857 1941)

The erythrogeni toxin a some strain produces a rash like that of sca let fever (Steven J 95 1957 1027 Aranow and Wood: J 119 1491 1942)

Staphylococcus toxi ha been used therapeutically after alteration to the toxoid by incubation with 0 3% formaldehyde the toxoid does not produce necrosis but does bring about significant, though not great, increase of tibody titer (Dolman CanadPHJ 24 126 1922 JInfectDis 55 172, 1934 Lancet 1 306 1935) Benefits in sycosis a d furunculosis were laimed by Connor and M Kie (BJD 46 20 1934) and i arious conditions due to staphylococci (Connor BMJ 2 1195, 1935 Edit. J 104 502, 1431 1936) It is without alue in acne (Whitby Lancet 1 1464 1936) See Anderson and Stokes (ADS 40 382, 1939) Prior to the introduction of the antibiotics, I used the toxoid commonly in cases of infectious eczematoid dermatitis, especially of the hands. Goodman (ADS 47 841 1943) recommended combination of toxoid and acein Antitoxi neutralizes staphylococcus toxin (Joyner nd Smith SGO 63 1 1936) diminishes the skin reaction t injections of toxin (Kenton AmJP th 16 185, 1939) and i of alue in septicemia (Rigdon and Stookey Surg 12 656, 1942) How er at present the immunologic approach in staphylococcic disease is seemingly obsolescent Little confidence ca be placed in ccines, utogenous or stock. In staphylococcic infection nowadays, reliance is placed on surgery hen ppropriate, control of inoculation, and antibiotics gi en topically or systemically

The unit of peni ili n was originally described in terms of ts capacity to inhibit growth of the Oxford strain of staphylococcus. Experien e with the use of the antibiotic soon showed that some strains either are or become penicillin resistant. Resistance could be creased b ult vati g the organi ms n reasi g c ncentrat on of penicillin, but when they were recultivated in ordinary bouillon the resistance lost (Todd and Turner BMJ 1: 111 1945) Resi tant strai were found t produce pen cillinase and from 100 cases of staph lococcic infect on, 38 resistant stra ns were cult v ted,

28 of which were obtained from patients who had received penicillin (Barber: BMJ 2: 863, 194) Resistant strains may be carried in the nasopharynx of ward nurses (Forbes BMJ : 500 1949) Resistant strains appear to be on the increase, so that the clinical value of penicillin may be decreasing according to Sherris and Florey (Lancet 1: 300 1951) These investigators thought that resistant strains are significantly less often associated with signs of inflammation and suppuration than the sensitive strains.

Aureomycin is usually effective against penicillin-resistant strains (Nichols and Needham: PSEBM 71: 300 1949) Terramycin and Achromycin are also excellent. Strains resistant to these are usually also resistant to penicillin but the reverse is not necessarily true (Finland and Haight AI tM 91: 143, 1953) See Treatment, antibiotics

Clarification of the properties of strains related to the dermatoses caused by staphylococci is by no means complete No epidermonecrotizing agency has been described yet pure cultures of *Staph aureus* are often obtained from purely vesicular or bullous lesions.

STAPHYLOCOCCIC IMPETIGO

Symptoms.—Staphylococcic impetigo is an acute superficial usually primary infectious dermatitis characterized by the rapid development of blisters filled with clear yellowish fluid appearing on normal looking skin or on top of red spots. When the bullae enlarge they become flat sometimes with depressed centers. They vary in size between those of a pea and a dollar piece or larger Differing from the ephemeral blisters of streptococcic impetigo the bullae of staphylococcic impetigo usually persist for a period of days. After they have ruptured the lesions become covered with thin, flat varnishlike crusts of a gray or brown color easily distinguished from the thick crusts of the streptococcic disease In older children and adults, the disease occurs chiefly on the face and neck In babies the folds are preferred neck, axillae and groins and lesions may develop all over the body which may be covered with large readily rupturing bullae a condition designated pemphigus neonatorum. Or staphylococcic impetigo may present circular or reniform lesions consisting of flat blisters and crusts about a zone centrally healed, so simulating circinate tinea (Epstein ADS 42 840 1940 44 317 1941 WiscMJ 40 383 1941 DZtschr 70 328 1935)

Lesions appear singly or in crops. Itching is annoying and scratching leads to autoinoculation The disease is typically a hot weather one and accounted for considerable morbidity in military personnel in humid tropical climates, where flexural (D Avanzo ADS 52 28 1945) as well as facial involvement was common

It is not unusual for impetigo to extend from the skin onto labial mucosae or into the nostrils (Montgomery JCutDis 28 445 1910) Impetiginous stomatitis may affect the inner surface of the lips and cheeks and spread onto the gums and tongue (Cushing Med 21 421 1904)

Impetigo due to an intensely hemolytic strain of staphylococcus may take the form of unusually itchy small superficial strongly erythematous lesions with little vesiculation. Small blebs, fragile and with a bright areola, typify streptococcic disease as a rule (Tachau BJD 50 113 1938) see Streptococcic impetigo

Large bullae sometimes single may occur as the manifestation of impetiginoid staphylococcic disease. This may affect the axillae or groins and is seen often in the Tropics (cf Pemphigus neonatorum and Pemphigus acuta)

BOCKHART'S IMPETIGO is superficial staphylococcic folliculitis, pustular from the onset (Bockhart MonatshPrakD 6 450 1887) Impetigo is a common complication of contact dermatitis, atopic eczema pediculosis capitis and scabies as is also infectious eczematoid dermatitis. Impetigo of the buttocks is usually scabietic Mucous membranes are sometimes affected by extension from the external sites.

ACNE NECROTICA MILIARIS of the scalp is a form of folliculitis which constitutes a typical clinical entity probably due to staphylococci (Lane ADS 28 10 1933) The patients are generally of middle age The lesions are discrete isolated and itchy Pruritus is intense being disproportionate with the visible disease. There may be perhaps 10 to 100 lesions. Before excoriation,

which is their prompt complication they are tiny vesicopustules justifying the name pustular perifolliculitis (Ormsby) Perhaps because of excoriation they leave little scars. If the disease persists and is persistently excoriated the hair may become thin as a result of alopecia cicatrisata. Seborrhea plays no important role in etiology Montgomery (ADS 36 40 1937) demon



Fig. 373 —Impetigo. Early unruptured bleb on helix.
Fig. 374 —Impetigo.



Fig. 375.—Impetigo.



Fig. 376.—Impetigo contagiosa, unusually severe. (Dr L W Ketron)

strated ulceration between adjacent hair follicles with a serosanguineous crust and a moderate infiltration mainly of lymphocytes extending into the mid cutis. Numerous staphylococci were seen at the margins of the ulcer Applications of ammoniated mercury may cure these patients. Staphylococcus toxoid antibiotics, and eradication of foci of infection, especially prostatic are sometimes effective measures. Daily application to the lesions of 10% am

moniated mercury in Carbowax 1500 and the diet appropriate for acne may be recommended. Bichloride of mercury 0.1% in 70% alcohol was approved by Wright (ADS 60: 468 1949) Response to antibiotics has been disappoint



Fig 277.—Impetigo. (Dr J Lama Calloway)



Fig. 278.—Impetigo, staphylococcic.



Fig 279.—Impetigo (Dr J G [illegible])



Fig. 280.—Impetigo

ing for the disease usually relapses when they are discontinued (Stritzler et al. ADS 64 464, 1951) An oxyquinoline antiseptic such as Ung Quinolor is sometimes helpful Pruritus limited to the scalp often responds to cortisone.

Etiology—Both staphylococci and streptococci have been recovered from impetiginoid lesions. Impetigo ' from the Latin an attack, is a clinical name devoid of etiologic connotation. Epstein, culturing 318 cases of im petigo found only staphylococci in 166 only streptococci in 7 both organisms in 143 and none in 2. Carefully reviewing the findings of others he noted that the particular bacteriologic technic influences the results. Mixed infections are common, as exemplified by the report of Cruickshank (Lancet 2 275 1941) who found in 23 cases Lancefield A streptococci in 15 and *Staphylococcus aureus* in 18 Epstein (JID 3 223 1940) fulfilled Koch s postulates by experimentally producing circinate impetigo with staphylococci. See also Bigger et al (BJD 56 55 1944) whose selective cultural methods revealed staphylococci in 97% of 130 patients, streptococci in 32% staphylococci only in 67% and streptococci only in 2%

Pathology—The epidermis is edematous and somewhat thickened. The roof of the bulla is formed by the stratum corneum The cavity is filled with serum in which are found degenerated epithelial cells, leukocytes and a few lymphocytes. Numbers of cocci may be found these are likely to be at the border of the bleb The dermis is inflamed moderately



Fig. 121—Impetigo of the fingers The forefinger lesion has almost healed. The middle-finger lesion has an acti edg The ring finger lesion is fresh.

Diagnosis—In contact dermatitis the vesicles are small, closely grouped and itchy In pemphigus the eruption is not confined to the face bullae develop as such, and the patients are adults. The presence or absence of pediculosis or scabies must be determined.

Prognosis.—Response to treatment is usually good. Fatal cases occur in babies. Reinfection may occur Autoinoculation prolongs the course. If scabies is present it must be treated promptly and vigorously with temporary disregard of cocci. If a case proves unduly rebellious, focal infection should be eradicated In an extremely hot, wet environment, the disease may be practically incurable

Treatment.—One may wipe the lesions gently and anoint them liberally with a 2% ammoniated mercurial paste, which should be reapplied several times daily Too strong an ointment is a mistake to be avoided. Sulfathiazole ointment was highly recommended by Winer and Strakosch (J 118 221 1942) and others it is a hazardous sensitizer A microcrystalline sulfathiazole paste may cure overnight according to Harris (J 121 403 1943) Penicillin oint ment 500 units per gram in a lanolin and petrolatum base was thought to be comparatively tidy and often efficient (Gold BMJ 1 1952 1945) but penicillin is no longer applied topically because of its now well known irritant and sensitizing potentialities.

Figs. 282 and 283.—Impetigo, staphylococcic.



Fig. 284.—Palmar lesion of impetigo, showing excoriation and intense superficial dermatitis.

The ointments in current use are tetracycline neomycin some other antibiotics, and Vioform. When an ointment is prescribed it is to be applied gently and on reapplication grease and débris should be wiped away gently with benzine or mineral oil on a cotton pledget Since without bacteriologic study which takes 24 hours and is more or less expensive one does not know what parasites are present—although an experienced clinician makes a canny guess—I generally combine 0.6% Chloromycetin with Vioform Cream and am only occasionally disappointed

If a case is rebellious, it is good practice to utilize the systemic effects of antibiotics because of the hazard of nephritis. Acute nephritis is a recognized complication of impetigo presumably when it is streptococcic (see p 282) Since tetracycline is so effective and so innocuous when given in modest doses for the few days during which it is needed I give it nowadays to almost every patient

Occlusive treatment, preventing autoinoculation during the few days needed for a given lesion to heal, has been highly recommended (Newman BMJ 1 823 1933) Metaphen 0.2% in collodion may be used for this purpose (*Hollander and Hecht AmJDisChild 48 269 1934*)

Gentian violet is unsightly but often effective (Sutton J 110 1733 1938) The caustic effect of silver nitrate often does more harm than the micrococci. Cool compresses moist with 1:10 000 $HgCl_2$ or 1:6 000 $KMnO_4$, may beneficially be applied for say 15 minutes 5 times a day Patients should be instructed as to the inoculable nature of the disease and the avoidance of autoinoculation a 7 year-old can be induced to keep his fingers off

Pemphigus Neonatorum (Ritter's disease neonatal dermatitis; superficial coccic dermatitis in infants) is an impetiginous, usually staphylococcic dermatitis in infants, in whom the infection is a serious matter It may begin with localized redness, which gradually spreads until the major portion of the body is involved. Or it may begin with wrinkled yellowish, desquamative lesions, or easily ruptured bullae or both, which appear in crops and spread widely Mucous membranes may be attacked. In the cases of Carter and Osborn (BMJ 1: 463 1930) the laundry was the source of the infection, and areas touched by unclean clothing were first affected. The desquamative process may be severe with the development of an oozing eczematoid condition. Folliculitis, furuncles, and deep abscesses may develop. The stools are loose and green and contain *Micrococcus*. Recovery or death generally ensues in from a fortnight to a month.

Cole and Ruh (J 63 1159 1914) are among the many who have confirmed the staphylococcic nature of the disease which has nothing to do with the diet The spread of organisms is subepithelial, a difference from the intraepidermal spread of adult impetigo The absence of papillae in infants skins renders this easier than in adult Streptococci apparently caused the 4 cases of Cannon et al. (ADS 4 834 1940) The pathogenic bacteria reach the infants usually from nasal carriers among the personnel who handle the children (Allison and Hobbs: BMJ 2: 1 194)

PROGNOSIS.—Almost half of v Ritterhsein's patients died. The outlook ultimately depends on the treatment *which must be instituted promptly and must be appropriate* It is possible to inoculate staphylococci so widely by smearing a baby with grease that recovery becomes impossible Epidemics vary in virulence

TREATMENT.—Prevention is possible when the source of infection has been determined. Aseptic noncleansing technic significantly reduced the incidence of impetigo neonatorum at the Philadelphia General Hospital (Ritter UCutRev 45 460, 1951) Oily preparations are worse than useless, but the immediate and early evacuation of blebs and the *careful* injection into them of 20% silver nitrate have been reported effectual. Supportive measures are indicated The % aqueous solution of gentian violet is of great service Hart (BJD 50 118 1938) used mercurochrome permanganate baths and dusting powders; he emphasized the necessity of opening the blisters and keeping the surface dry A cradle with lights to provide radiant warmth, along with good ventilation, is useful. Undermined epidermis should be removed so that the antiseptic may have access to the place where it is needed. Daily inspection is necessary

Penicillin by injection saved the patient of Callaway et al. (JPed 28 39 1946) after other therapy failed. Penicillin ointment succeeded in 14 cases of Kendig and Fiske (J 129 1044 1945) Penicillin resistance accounted for the tragic course of an epidemic reported by Lee et al. (JPediat 41 159 193) in which 1 cases of impetigo were accompanied by 10 cases of severe staphylococcic paronychia, and half of the latter group died. A seemingly trivial infection with an insensitive strain may eventuate in serious complication (Forfar et al BMJ 1 0 1953) The correct antibiotic must be selected by means of sensitivity tests. Tetracycline is usually promptly effective It may be sprayed on a 1% aqueous solution and given by mouth at the same time It should not be overdosed.

See Falls (JInfectDis 20 86, 1917) vesicula staphylococcic dermatitis Zahen (ADS 24 830, 1931) Swendson and Lee (J 96 *481 1931) 2 epidemics, dry treatment Poule and



Fig. 235.—Bockhart's impetigo. (Dr F Ronchese.)

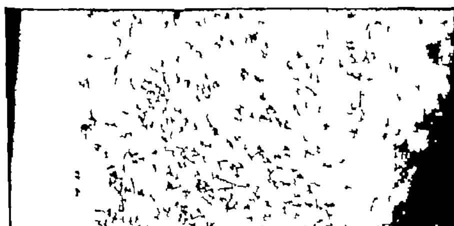


Fig. 236.—Bockhart' impetigo.



Figs. 237 and 238.—Acne necrotica miliaris tiny itchy, follicula lesions of the scalp. (Montgomery ADS 36 40, 1937.)

Whittle (Lancet 2 1323, 1935), transmission by personnel or impedimenta; Kendall and Aegerter (JPed 15: 733, 1939) Ritter' disease; Flood (AmJDisChild 58 831, 1939) nursing technic Denians (BMJ 1 623 1943) bullous cases, doctors and nurses as carriers Forfar et al. (Lancet 1: 884, 1958) erythromycin with streptomycin effective, same strains of organism in nursing staff and infants; Edmunds et al. (BMJ 1 990 1955) nasal carriers in staff are main source of pathogens in newborns

Desquamative Erythroderma of Infants (Leiner's Disease) is not to be distinguished from the mild form of staphylococcic exfoliative dermatitis of the newborn. It begins on the buttocks in many instances and becomes generalized with lymphadenitis but without vesiculation. It was described as a self limited disease by Lereboullet and Bohn (BSocPédiat 33: 373 1935) and the infant does better when placed on a low fat, high protein diet (Hill: J Pediat 4: 426 1934) Staphylococci were cultivated from the lesions and from the bladder in several cases by Sperk (abs J 7 : 1764, 1914) Gastroenteritis accompanies the disease or precedes it.

See Leiner (BritJChildDis 5 244, 1908 ArDuS 89 65, 1908) Cole et al. (AD& 70: 443 1954) review suggesting Leiner's disease is modified, subacute form of Ritter's, both due to staphylococcus, to be treated with antibiotics and vitamin B complex Crotty (AD 71: 647 1955), 4 cases with protracted diarrhea and secondary anemia, responsive to antibiotics and transfusions of whole blood



Fig 289 — Acute pemphigus" the boy recovered (Dr H D McClure.)



Fig. 290 —Pemphigus neonatorum this child died. (Drs Morrow Miller and Taussig)

INFECTIOUS ECZEMATOID DERMATITIS

Synonyms.—Pustular eczema (many cases) Impetiginous eczema (some cases) Superficial staphylococcic dermatitis.

Symptoms.—Infectious eczematoid dermatitis is characterized by erythematous, vesicular pustular or scaly circumscribed plaques of acute dermatitis which commonly develops from coccic complication of mechanical or

chemical trauma. The exposed parts are those generally first affected. The initial lesion may be a vesicle pustule or an inflammatory scaly or crusted papule The vesicles are not so closely placed and are larger than in an acute vesicular contact dermatitis The lesions are asymmetric as a rule. The eruption spreads by autoinoculation and occurs in circumscribed patches of moderate size which enlarge by peripheral extension. Vesicles soon break to form an oozing patch which extends. New foci begin as clusters of vesicles. The epidermis at the periphery of the lesion is usually undermined, detached or raised by collections of seropurulent fluid which may contain much fibrin so that a thin ridgelike crust forms about the periphery There is no tendency to involute centrally Itching is usually considerable There is usually lymphadenitis, particularly when the disease is widespread as it may be even to the extent of being universal. The disease is often associated with scabies, pediculosis, furunculosis, otitis, or other suppurative disorder such as an infected, ingrowing toenail It is commonest in active adults.



Fig. 191.—Infectious eczematoid dermatitis secondary to scabies. (Sutton J 75 976, 1920)

Etiology — Engman (AmM 4 769 1902) recovered the staphylococcus in pure culture from early lesions and from the surface and crusts of later patches. Experimental autoinoculation can usually be performed then the lesion begins as an erythematous patch which soon becomes moist and crusted.

It is thought that allergy plays some part (Sutton J 75 976 1920 Foerster WiscMJ 34 305 1935) The chronicity and rebelliousness of infectious eczematoid dermatitis distinguish it from ordinary primary staphylococcic infections and convince me that more than a primary infection must be concerned. Contact dermatitis is often the primary disease and contactants may require elimination before antiseptics attain lasting effectiveness. Foci of infection are also frequently concerned. Dermatitis of the hands (q v) an intractable and disappointing disease according to most medical literature has proved usually to be gratifyingly responsive if the aspects of contactants, parasites and foci are eliminated (Lane et al. J 128 987 1945 Sutton and Ayres ADS 68 266 1953)

Sometimes patients apparently fail to heal because of hypoproteinemia, anemia or chronic fatigue from anxiety or overingestion of caffeine The confused status of etiologic understanding was stressed by Kennedy et al (South MJ 46 707 1953) who took into account allergy autosensitization, overtreatment, and psychosomatic causes in an attempt to explain the recalcitrance of some cases.

Pathology —The papillae are swollen and congested There are slight acanthosis and edema of the prickle cells. Destruction is marked in the lowest



Fig. 292.—Infectious eczematoid dermatitis.



Fig. 293.—Infectious eczematoid dermatitis.



Fig. 294.—Dermatitis simulating Paget carcinoma but due to *Micrococcus aureus*.

layers of the stratum corneum which is undermined and detached and its elevated margins are frayed Abscesses are to be found in the upper region of the rete, and groups of cocci can be seen in them. Polymorphonuclear leukocytic infiltration is profuse.

Diagnosis.—In contact dermatitis, the eyelids are usually swollen and itchy and the flexures are involved by predilection; the disease is not primarily pustular but by secondary infection often is complicated by infectious eczematoid dermatitis. The impetigos occur generally in children their lesions are discrete and seldom involve the body and limbs. Staphylococcic impetigo differs little from infectious eczematoid dermatitis. Perhaps one may say that staphylococcic impetigo in the presence of contact dermatitis or focal infection is identical with infectious eczematoid dermatitis. The discrete pea to fingernail size deeply seated, painful not itchy pustules and crusts of ecthyma are distinctive Moniliids and other mycids must also be differentiated. They too may be complicated by staphylococcic parasitism

Treatment.—Greasy preparations are to be avoided, especially irritating ones, such as fungicides. Cole recommended hot 1:5 000 aqueous solution of potassium permanganate 20-minute soaks 3 or 4 times a day for 4 or 5 days. Radiant heat is useful. Gentle débridement is an important part of treatment Crusts must be removed so that antiseptics can reach the bacteria. Baths in bichloride of mercury 1 10 000 (4 Gm. in 10 gallons of tepid water) are useful and comforting but one must be alert to percutaneous absorption and mercurial intoxication (diarrhea) when bichloride baths are used. Wet packs of bichloride may be laid over lesions painted with gentian violet with satisfactory results, especially when both staphylococci and streptococci are present as they often are Foci of infection must be eradicated in resistant cases teeth, gums, sinuses, prostate and running ears are the commonest of these Hospital care is much to be preferred to ambulatory

Penicillin in large intramuscular dosage is quite efficient A common experience is to give penicillin with temporary benefit only to observe relapse soon after it is stopped. When this happens one may be confident that focal infection is significant. Contact irritation must also be eliminated. Chronic pustular dermatitis of hands and feet can often be cured when approached from this standpoint. Hopkins and Burky (ADS 49 124 1944) reported successful desensitization by intracutaneous immunization with staphylococcus toxin. Cooper (PaMJ 46 218 1942) also eliminated foci and used staphylococcus vaccine Bacitracin ointment 480 U per Gm., rarely irritates and often benefits (Miller et al. JID 10 179 1948) Tetracycline orally and topically is effective used in conjunction with potassium permanganate soaks or poultices. Cortisone and high protein diet may also help

X ray therapy is only rarely helpful. When vesicular dermatitis is not responsive to x ray staphylococci are probably causative

Jungle Rot was the G I name for this disease in the tropics, where heat, humidity and staphylococci, along with other factors perhaps, such as hygiene nutrition, and quinacrine produced much morbidity during World War II (Travis: MilSurg 97 224, 1945 Cohen USNMBull 42 1119 1944) When these patients were returned to the zone of the interior in a temperate climate, under conditions conducive to health they generally improved satisfactorily In some the lesions became chronic and lichenified see Lichen Chronicus Simplex.

FURUNCLES AND CARBUNCLES

Furuncles (Boils) are acute circumscribed, follicular phlegmonous inflammatory lesions caused by virulent staphylococci in the skin. Carbuncles are conglomerate furunculoid lesions involving not only skin but also subcutaneous tissue with suppuration, sloughing and the discharge of necrotic material through multiple openings.

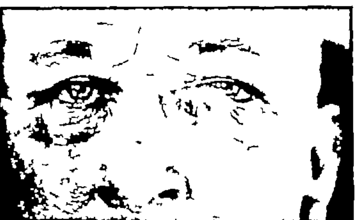


Fig. 296.—Acute staphylococcic cutaneous abscess.

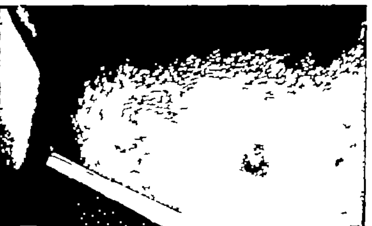


Fig. 294.—Boil on the neck. (Dr Stuart C. Way.)



Fig. 297.—Carbuncle of the nucha.



Fig. 295.—Carbuncle of the back. (Dr Clyde L. Cummer.)

In a furuncle the inflammatory process begins as a rule in the immediate vicinity of a skin gland or hair follicle. Furuncles may number from 1 or 2 to 50 or more and disease may be prolonged almost indefinitely by repetitious development of new lesions. The neck, axillae face buttocks, and legs are sites of predilection although no region is exempt. A lesion begins as an itchy acuminate pustule surrounding a hair As it develops the involved skin becomes smooth, tense and shiny painful and tender In a few days the tumor usually matures, and either comes to a head or becomes boggy and fluctuant. In some cases regression takes place before the occurrence of suppuration, and the lesion a *blind boil* slowly undergoes absorption On reaching maturity a boil generally ruptures spontaneously and a necrotic core is discharged, together with pus and serum Healing speedily ensues. In some boils the center undergoes necrosis but becomes tough stringy and tenacious. Such boils are of relatively small size extremely painful and less responsive to treatment than ordinary ones. They are due to strains of staphylococci which produce necrotizing toxin

Globose lesions developing umbilicated necrotic centers representing bacterial emboli and liquefaction necrosis and resembling acne varioliformis, were described by Balog (JID 5 107 1942) and attributed by him to metastasis from a primary suppurative focus. Compare sweat gland abscesses (p 278)

A stye is a furuncle of a lid margin gland The external type affects the gland of Zeis, the internal affects the Meibomian gland (Dunn WiscMJ 38 117 1939)

Carbuncles resemble furuncles but are larger and more painful and are accompanied by more systemic intoxication When necrosis occurs, their contents are discharged through several openings. The lesions are commonly single. They start with painful localized, erysipelas like induration, which gradually increases in size. The affected skin is dark red tense and shiny Suppuration occurs within from 7 to 14 days, but instead of a single central slough as in a furuncle, the tumor drains through a number of openings and the purplish summit presents a cribriform appearance The central portion of the lesion may undergo necrosis at several different points at the same time and a number of small sloughs form and are cast off or the entire mass may be involved at once with the resulting formation of a deep ragged ulcer This cavity fills up with granulation tissue and ultimately heals with more or less scarring Systemic intoxication may be severe even fatal, and metastasis and septicemia are possible complications. The sites of predilection are the neck shoulders, buttocks, and outer surfaces of the thigh.

Staphylococcic abscesses and cellulitis require mention. They generally fall to the surgeon rather than the dermatologist.

Staphylococcic gangrene is serious but uncommon. Of 5 cases involving the face, resembling erysipelas but becoming gangrenous 2 proved fatal reported by Stookey et al (J 103 1934) The dermonecrotizing toxin is the cause of gangrene (Stookey and Scarpellino SouthMJ 28 148 1935) The facial predilection, the violet color and the probable absence of pustulation were the features stressed by Troisier et al. (PresseMéd 44 801 1936) who estimated mortality at 75% Diabetes predisposes to this condition, which is not to be confused with the streptococcic disease it simulates, wrote Millett (J 112: 1143 1939), giving a bibliography Success in treatment may be obtained with antibiotics and careful control of the diabetes (Millett and Darby NEngJM 235 12, 1946)

Etiology—Pasteur (ComptrendAcadSci 90 1033 1880) described the cultivation of microorganisms from a boil

A puncture was made at the base of the small cone of pus at the apex of a furuncle on the nape of the neck. The fluid obtained was at once sowed. The next day the culture fluid had become cloudy and contained a single organism, consisting of small spherical points arranged in pairs, sometimes in

fours but often in irregular masses.' He demonstrated the pathogenicity of the germ he had cultured and recovered it from lesions produced by cultures in human volunteers.

The appearance of new lesions is not ordinarily due to septicemia, but follicles are infected exogenously. Ointments facilitate autoinoculation.

Certain factors predisposing to microbic invasion are generally recognized. *Of these diabetes mellitus, nephritis, and avitaminosis are the most important.* In every case of furunculosis the patient's urine should be examined. Occupational exposure to grease such as cutting oils also predisposes but furuncles, which multiply, should be distinguished from oil acne which is associated with comedones (Schwartz: PHRpts 56: 1947, 1941). Warmth, humidity and sweating render the skin especially vulnerable to staphylococcic parasitism, for they interfere with self sterilization by drying. In obstinate cases search should always be made for foci of staphylococci in sinuses, tonsils, teeth and urogenital tract. The influence of vitamins is *apparently consequential only in their decided lack,* although vitamins A, D, and C may have some therapeutic usefulness.

The seasonal peak of boils in Great Britain is October or November and most lesions are on the head, face and neck, seemingly the result of contamination by the fingers which transfer organisms from the nose (Whitwell and Sutherland: BJD 62: 109, 1950).

Pathology.—The inflammatory process involves a gland or follicle. The slough is composed of pus, fibrin and necrotic glandular and periglandular tissue. Changes in the dermis are those of acute purulent inflammation. In carbuncles, the infection is deeply seated, and the dermonecrotizing inflammatory process involves dermis and subcutaneous tissue.

Diagnosis.—The staphylococcus is readily found in the pus and may be cultivated easily. Erysipelas is not pustular. Anthrax is characterized by vesicles about a blackish necrotic center. Syphilitic lesions are less acute and painful by far. Iodide and bromide eruptions are distinguished from furuncles by history, culture and blood bromide testing. Acne is often confused with coccic parasitism, which of course can occur secondarily, but acne vulgaris is not a parasitic disease. The itchy acne caused by androgenic substances or ACTH would not confuse an alert observer.

Prognosis.—Recovery generally ensues within a few weeks. Lesions involving the face or scalp are especially dangerous. In elderly and debilitated individuals a virulent infection may prove fatal. The disease usually responds favorably to treatment, although recurrences through autoinoculation are common. Response to antibiotic therapy may be delayed because of resistance, but antibiotic sensitivity tests should dispel this difficulty.

Treatment.—Codeine may be required and should not be withheld. The urine and blood sugar should be tested. The value of vitamin preparations is highly debatable. Thyroid was given by Barnes (JClEndocr 3: 243, 1943) who explained his favorable results on the basis of improved skin temperature, tone and circulation. The only oral medication Sutton, Sr. used to prescribe was sodium citrate. In adequate amounts it tended, he felt, to hasten necrosis and liquefaction.

Limiting the ingestion of carbohydrate may be advisable (Kulchar: JChemother 14: 61, 1937). Dogs on a high starch diet suffered worse effects from experimental inoculation than controls (Lillsbury and Sternberg: ADS 35: 893, 1937).

Sulfonamides have been recommended but chemotherapy alone is inadequate when there exists an accessible collection of pus, which, as John Hunter taught, must be let out (Heling and Abel: AnnSurg 30: 238, 1940). Osgood (JPed 17: 740, 1940) claimed benefit from neoarsphenamine and sulfathiazole. Passive immunization by means of antitoxin has been tried. Stookey and Scarpellino (SouthMJ 32: 173, 1939) investigated dermonecrosis and were

able to help some cases by giving antitoxin, which has value in toxic cases. Bacteriophage was at one time well thought of by some authors it was applied as a moist compress.

Vaccine therapy stock or autogenous, has given me no satisfaction.

Dermonecrotizing toxin produces necrosis quantitatively related to the amount of toxin injected It is neutralized by simultaneous injection of immune serum *Toxoid injections evoke active immunity to toxin without* causing severe reactions. A course of toxoid therapy is often highly efficacious (Zernetol Surg 17 303 1945) although measurement of the staphylococcus antitoxin titer which does not change much has little clinical utility

Antibiotics given by mouth such as Achromycin, are effectual. Penicillin by injection is sometimes eminently satisfactory The dose should be large Some strains of staphylococci are not responsive and some cases of chronic furunculosis improve only temporarily If a given dosage does not yield results, one should increase it greatly before assessing the agent as useless in that case *Since penicillin does not influence immunity toxoid may be ad*visable also in difficult cases of furunculosis. Direct injection of penicillin into and about the infected tissue was thought by Kenney (Surg 21 588 1947) to be especially effective A million units in 5 cc. saline adding 5 cc. procaine solution was injected about the periphery of the carbuncle so as to lay down a barrier of the antibiotic outside the indurated region by Dale and Haug (J 149 527 1952) this treatment along with penicillin intramuscularly bed rest and hot wet packs, was assessed as valuable by these authors. I have never used local injections of penicillin. Penicillin ointment is not satisfactory but an occlusive dressing with Aureomycin or Terramycin ointment may work well Nightly inunction of the whole body with a thin layer of Vioform Cream may cure furunculosis.

Immobilization is important, and this may be accomplished in small lesions by the use of collodion, protective dressings and perhaps a sling Fraser (BMJ 2 894 1935) recommended an elastoplast occlusive dressing which protects, relieves pain and enables a patient to continue his work.

Mild antiseptics applied in the form of blotterlike moist poultices may be employed A good plan is to paint the lesions and their periphery once daily with diluted tincture of iodine or 1% gentian violet in alcohol to prevent autoinoculation then to apply a large gauze pack moistened with half and half glycerol and alcohol Glycerol inhibits by partially destroying the dermonecrotizing toxin (Smith Brit J Exp Path 18 265 1937)

Incandescent lamps, 500 watts, are valuable as sources of radiant heat especially in early stages. Ultraviolet light is worthless in this condition.

Roentgen therapy as it applies to inflammation is discussed in the chapter on Treatment (q v) The effect of electromagnetic energy is not on the organism. It is usual to give small doses. The more acute the lesion the smaller the dose Epstein teaches.

On the back of the neck and in the axilla, MacKee pointed out one suberythema dose may prevent the development of new lesions It may be necessary to depilate the parts in order to effect a cure and this should be accomplished with fractional doses avoiding erythema. Soon after the treatment the patient is likely to be worse, but within 48 hours the pain will have disappeared In some cases the induration is gradually absorbed, while in others the lesion softens and discharges. When the lesion is treated before discharge and while in the indurated stage, x rays cause rapid regression. X ray treatment of lesions of the face is curative painless and safe, with much smaller morbidity and mortality rates than surgery yields (O'Brien NEngJM 220 917 1939) Cannon (SouthMJ 38 106 1945) recommended the following measures 400 to 600 r radiotherapy including a good margin daily irrigation of the region with 5% phenol a thick cotton dressing embodying a paste composed of fluidextract of ergot 6.0 phenol 0.6 and zinc oxide and starch 4.0 of each in cold cream the probing of openings with 50% phenol and intramuscular injections of colloidal manganese or sterile milk.

A boil can perhaps be aborted by the early local application of mercurial plaster or of tincture of iodine. One may hasten its maturity by the aid of hot moist antiseptic dressings.

Many authors have insisted that a boil should never be incised. There are exceptions to this generally wise rule A tiny itchy and painful follicular pustule will progress considerably unless it is aborted. If the point of a scalpel is moved through the undermined epidermis across the follicle mouth so as to penetrate something less than half of the thickness of the dermis, drainage will be made adequate I should then apply *tetracycline ointment* and an occlusive dressing Extraction of the infected hair is an error for this procedure gives the staphylococcus free access to subdermal spaces where an abscess is the least of the prognosticable evils. It is especially dangerous to extract infected vibrissae *Squeezing a lesion accomplishes the same bad effects.*

A surgical attack upon carbuncles is occasionally to be recommended. Prior to penicillin, crucial incision in the early stage was popular a radical *effort being made under gas or pentothal anesthesia (Fantus J 103 1066* 1934) The flaps were laid back the pockets cleaned out and the wound packed with moist iodoform gauze or similar material. Complete and early excision of the infected mass has been advocated but this is rarely necessary Excision of a carbuncle *may stop pain and intoxication dramatically*

The hazards of carbuncles of the face have been stressed by many writers, cavernous sinus thrombosis being a dread complication. This occurred once in 31 cases reported by Totten (WestJSOG 43 609 1935) accounting for *one of the 3 fatalities. Conservative treatment in contrast with surgery led* to lower mortality rates, lower morbidity rates and better cosmetic results (Ayres et al. J 108 858 1937) See Edit (J 109 278 1937) Elliott (IllMJ 72 491 1937) Maes (AnnSurg 106 1 1937) 20 fatal cases, emphasizing avoidance of incision Berman (AmJSurg 40 419 1938)

In recurrent cases find the focus of dissemination of the virulent germs this focus may be inconspicuous. There seems little doubt that susceptibility is variable, for some individuals are infected time after time, and others rarely suffer Guiding principles in the treatment of recurrent furuncles should include attempts to keep the skin dry clean and free from irritation, to eradicate foci of infection, and to raise the general resistance of the patient (Anning BMJ 1 721 1953) The nose is the major source of the pathogen in carriers and should receive attention in recalcitrant staphylococcic infections of the skin (Tulloch BMJ 2 912, 1954) See Edmunds et al. (BMJ 1 *990 1955)*

FOLLICULITIS

Folliculitis is *often staphylococcic differing from furunculosis mainly in* depth and severity of inflammatory reaction about the hair or sebaceous follicles. A solitary lesion, itchy acuminate and pierced by a hair may comprise the whole disease or such lesions may affect a considerable area or may *be widespread over the hairy regions of the body* Sycosis is described elsewhere. It is not remarkable when the infection penetrates to the subcutaneous layer so that an abscess develops. This is often seen on the dorsa of the fingers, and the lesion may have a collar button shape with a small purulent bleb on the surface a tiny hole through the skin and a pocket of pus beneath requiring incision and drainage Folliculitis often results from autoinoculation especially as the result of smearing staphylococci about by the application of greases. When folliculitis is chronic focal infection must be sought out and eradicated. Treatment is as for furunculosis (q v) or for impetigo (q v) compare Bockhart s impetigo

Staphylococcic infection of sweat follicles in infants was described as periporitis staphylogenes by Lubowe and Perlman (ADS 69 543 1954) The lesions consist of minute pinhead to pea-sized, disseminated papules and

pustules, especially over the scalp forehead neck, upper half of the chest, shoulders, upper extremities and back They may be of different sizes and different stages of evolution, tiny firm erythemtous nodules that are deeply situated and capable of becoming pustules or abscesses. Temperate dry surroundings help to bring about cure which is sought in much the same manner as in the treatment of furunculosis (q v) Multiple sweat gland abscesses of infants was the title of the article by Mopper et al. (AD 71 177 1955) in which they described the dome-shaped nodules representative of staphylococcic parasitism inoculated into sweat pores.

Rosacea like Folliculitis is a clinical entity which I have not seen described elsewhere. It closely resembles rosacea, but may be quite itchy which is a difference and the shallow pustules, surrounded by considerable erythema, may be recognized as follicular when examined under magnification. This chronic disease may be discrete or confluent. It responds to antibiotics and to elimination of foci, usually oral, occasionally genitourinary Vioform Cream may be helpful, or 2% salicylic acid in 5% ammoniated mercury ointment as Staley showed me

PYODERMA FACIALE

Pyoderma Faciale was described by O'Leary and Kie land (ADS 41: 451 1940) as an explosive eruption of deep pustules on the face in you g women who have had, or perhaps have not had, preceding acne. Tunneling abscesses, thick greenish pus, pain and tenderness, and disfiguring keloidal scars are characteristic. The patient is often under weight, anemic, and amenorrheic, but tuberculosis has not been found. Antianemic and vitamin therapy appears to be indicated. X ray therapy may be used. Very large doses of penicillin may do the job when modest ones do n t. Compare Hidrade iti axillari suppurati a.

See case reports (ADS 42 1133, 1940; 43 572, 744 1941 50: 418, 1944; 54 349, 573 1946); Reuss (JLabClinM 28 1032, 1943)



Fig. 199 —Pyoderma faciale. (Cole nd Driver: ADS 43: 572, 1941.)

CHANCRIFORM PYODERMA OF THE FACE

Solitary o few in umber the lesions evolv in a few weeks from minute papules into ulcers resembling the syphilitic chancre. The base is indurated, smoothly ulcerated, but superficial, and the bord is not elevated. Staphylococcus aureus was found and sulfathiazole was apparently curative in the case of Kra tz (DWehn 109: 1203, 1939) See Hoffmann (AfDuS 170 403, 1934); Stryker (ADS 4 447 1940); Laymon et al. (AmJSyph 38: 57 1954)

Ulcus Migrans.—A remarkable case with lesions of a spreading and undermining nature, simulating large sores of acne co globata on the chest and shoulder yielded an unusual staphylococcus (Hicks: BJD 62 1 4 1950) There was no lymphadenitis, fever or leukocytosis. Develop g from pustule on n Arab boy's back in a period of 2 years, a bizarre arcuat ulcer prod ct ve of depigmented scarri g was observed by MacDonald (BJD 50: 606, 1938) wh cultivated from the lesion *Staph. aureus.*

GAFFKYA TETRAGENA INFECTION

Pathogenicity of this organism which is one that possesses ordinarily only slight virulence and becomes invasive only when the resistance of the host is reduced, has received consideration from Reimann (JClinInv 14: 311 1935) and Zeligman a d Slesel (ADS 65: 332, 1953) The latter reviewing the literature noted that some 170 cases of *G tetragena* infection have been recorded. They reported a carbuncular lesion caused by it. This was responsive to Terramycin. Infections with *G tetragena* generally resemble the local suppurative or septicemic diseases caused by *M aureus* a closely related organism. Cases have been ascribed to it of septicemia, arthritis, meningitis, endocarditis, pneumonia, prostatitis, empyema and glomerulonephritis.

In a recent year period I had 7 cases in which *G tetragena* was the sole or predominant organism. The lesions were impetiginoid acute and pruritic and in most instances were incited by mechanical or chemical injury followed by secondary infection. *M aureus* wa also present in 3 of the 7 cases. All were promptly responsive to tetracycline oxyt tracycline or chloramphenicol used topically

STREPTOCOCCIC INFECTIONS

A basic serologic classification of *Str pyogenes* (equivalent to group A hemolytic) was made by Griffith (JHyg 34: 54, 1934) See Lancefield and Hare (JExpM 61: 335 1935) regarding classification. The epidemiology of streptococcic infections wa well delineated by Bradley (BMJ 1 733 1938) See Mackie (EdinMJ 47 466 1940) regard ing herd infections. When any part is inf ct d with streptococci pathogens are plentiful as transients on healthy areas (Martin: BMJ 1 45, 194)

Str viridans and nonhemolytic streptococci, apart from rare strains, are f little sig nificance as human pathogens. One strain of *Str pyogenes* may in any given epidemic produce angina, scarlet fever erysipelas, cellulitis, lymphangitis adenitis, otitis stasit tis, meningitis, puerperal fever and septicemia, in accordance with the unitarian hypothesis. Therefore the tendency is to discard specific names for strains which depen l on morphology and cultural characteristics. Most hemolytic streptococci are identifiable by a specific carbohydrate substance and fall into Lancefield Group A. This group was divided into about 30 subtypes by Griffith. Bradley described single-strain epidemics in various semi isolated groups. The rash of scarlet fever is fortuitous, he stated, but each type of the disease streptococcic infection, is an index of the prevalence and an indicator of the ex stence of the pathogen in the community The aggregate of the clinical manifestations probably represents about half of the actual streptococcic morbidity The great bulk of treptococcic disease is probably zymotic and associated with an increased carrier rate enhanced parasitism being at any given time due to one or few serologic types of the organism. Droplet infection is common as well as milk borne but comparatively a timate contact is required; less important is casual contact. The tempo of transmission s slow and is due probably to transference via immune carriers A period of from 5 t 10 days elapses between infection and detection of it. Immune carriers are probably infected for only a brief period, but these are probably more important epidemiologically than persons with chronic foci. A type specific epidemic runs its course and dies out spon taneously Persistence of the in idence of infections and recurrences point to the ntro duct on of a new type of streptococcus.

STREPTOCOCCIC IMPETIGO

Symptoms—Streptococcic impetigo is characterized by superficial lesions covered with thick crusts honeylike and of a yellowish color noted Epstein (WiscMJ 40 383 1041) Compare staphylococcic impetigo The streptococcic disease starts as a red spot, on top of which a thin walled blister develops and this may so rapidly collapse as to be missed In simple cases a few crusted lesions are present In severe cases the lesions become confluent so that the face may be covered by masses of discharging eroded crusts, the original yellow color perhaps changing to a dirty brown from admixture with blood. Regional lymphadenopathy may occur Since the disease is superficial no scar results although circumscribed erythema or brownish staining may persist for some weeks. The favorite location is the face but the neck, hands and scalp are also frequently affected Any location may support the infection, especially when it is secondary to another dermatosis. On the fingers or toes, where the corneum is thick, one finds rapidly enlarging painful bullae which the dermatologic consultant often sees after the patient has erroneously been treated for tinea. The latter itches rather than hurts, and its progress is less precipitate

Ecthyma involves dermonecrosis, and is related to streptococcic impetigo as furuncles are related to staphylococcic impetigo



Fig. 300.—Streptococcic impetigo with "stuck-on crusts."

Fig. 301.—Erysipelas.

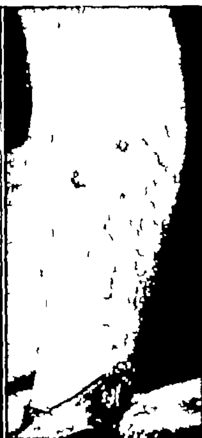


Fig. 302.—Ecthyma.

Etiology.—Streptococcic impetigo occurs either as a primary disease or as secondary infection of any itching dermatosis, such as scabies, dermatitis venenata or infantile eczema. As a primary disease its incidence is seasonal maximal in the fall and parallel with other streptococcic diseases. Comparatively close contact is requisite for transmission. The organism is hemolytic. Mixed infections with both streptococci and staphylococci are common see p 266

Treatment.—The principles involve gentle débridement and isolation of the lesions, the use of suitable antiseptics, and prevention of autoinoculation and spreading. Ammoniated mercury ointment, 2% removed by benzine at the times when it is refreshed, is often effective. Sulfonamide ointments, hazardous with respect to inducing sensitization, have been used effectively but are not recommended nor is penicillin ointment in the light of current views. Aureomycin Bacitracin, Terramycin, Neomycin, dihydrostreptomycin or Chloromycetin ointment is quite satisfactory as a rule. Compare treatment of staphylococcic impetigo and infectious eczematoid dermatitis. Cool compresses, using 1 10 000 bichloride of mercury or 1 5000 $KMnO_4$ are also useful. Tetracycline may well be given orally for a few days.

Impetigo and Nephritis.—Increasing stress has been given the fact that streptococcic dermatoses are followed by nephritis with consequential frequency so that impetigo may not rightly be considered trivial

Stiell (Pract 100: 368 1918) described 5 cases of severe acute nephritis complicating impetigo. In the patient of Cleveland (CanadMAJ 24: 272, 1931) the widespread application o mercurochrome to a neonatal impetigo may have resulted in nephritis from mercury rather than from coccic toxins. Studying cases of acute nephritis in children, Sutton (SouthMJ 27: 708 1934) found that more than one-fourth of them followed severe impetigo. The prognosis of such nephritis is quite good Silvers (NYSJM 39: 1093, 1939) decided after reviewing the literature, yet the kidney injury can be severe. He quoted the experience of Southby and Stanton (MJAustral 13: 127 1926) of whose 103 cases of nephritis, 29 followed tonsillitis, 17 followed impetigo, 15 followed measles, 11 followed pneumonia and 27 were of undetermined cause, while Hill (AmJDisChild 17: 270, 1919) attributed 4 of 51 cases of nephritis to impetigo. Of 1 4 cases of acute nephritis impetigo preceded 34% a higher proportion than was preceded by tonsillitis in the series of McCullough et al. (JPed 38: 346, 1951) and nephritis was fatal in 1.5% of the victims.

In impetigo the white blood cell count e ceeded 10,000 in 24 of 25 patients noted by Towle and Swartz (ADS 9: 551, 1924)

The complication of nephritis is not related to the severity of the dermatitis that induces it, according to Futcher (AIntM 65: 1192, 1940) He recognized it as being more common in children but described its occurrence in 11 adults ranging up to 60 years of age, one of whom had impetigo, the others pyodermas or erysipelas. Edema was the first symptom and appeared within 2 to 6 weeks after the dermatitis appeared. Albuminuria lasted longer 12 months in 7 of these 11 patients. Beta hemolytic streptococci we e cultivated from the skin in 7 of his 11 cases. An epidemic of impetigo has been known to be followed by numerous cases of nephritis. Callaway and O'Rear (ADS 64: 159 1951) observed that 36 of 73 cases were preceded by pyogenic dermatoses, and, confirming other uthorities, stressed th wisdom of treating skin infections early and vigorously in o der to prevent thi serious complication.

Antibiotics given systemically are therefore justified if a case of impetigo does not respond to topical therapy promptly and satisfactorily When penicilli was used in an extensive series of beta hemolytic streptococci infections in children by Breese (J 152 10 1953) the incidence of complicating rheumatic fever or acute glomerulonephritis was exceptionally low

Cortisone is said to be effectual in poststreptococcic states u responsive to antibiotics, just as it is helpful in heumatic fever (Doerner et al.: J 146 641 1951)

ECTHYMA

Symptoms.—Ecthyma is manifested by the formation of small, discrete flat, painful pustules which heal reluctantly and may be followed by slight scarring and pigmentation. A child is the usual patient. The legs and thighs are the sites of predilection, although no region is exempt. The lesions, ranging in number from 1 to 20 or more are irregularly oval sharply defined and have reddish areolae. They begin as small yellowish pustular excavations, which enlarge. The exudate desiccates, forming thick, adherent, brownish

crusts. The bases are raw and tender On healing the crusts drop off but the disease may be continued indefinitely by the development of new lesions. Slight lymph node involvement is usual. The lesions sometimes persist for weeks, unless correctly treated.

Etiology—Streptococci, perhaps secondarily complicated by *Staphylococcus aureus*, are the cause Ecthyma was experimentally produced by inoculation of streptococci into injured skin by Bizzozero and Leone (AfDuS 176 16 1937) Uncleanliness poor hygienic surroundings and inadequate diet are also sometimes concerned. Trauma and insect bites are common exciting causes. The disease is readily autoinoculable.

Pathology—The lesions are shallow abscesses. The dermis is swollen, infiltrated and perhaps necrotized Purulent inflammation and exudation are seen in sections.

Diagnosis.—In flat pustular syphilids lesions are more numerous and disseminated, edges of ulcers are abrupt there is little pain and crusts are bulky and greenish while other signs of syphilis are usually apparent

Ecthymatous lesions have been described under a multitude of names see Ulcer tropical Shallow ulcers of the extremities yielding streptococci and staphylococci were called pyoderma ulcerosum tropicalum by Alpins (MJAustral 1 30 1943) while dermatitis cupuliformis was the title given tropical ecthyma characterized by the evolution of cupuliform nodules which underwent ulceration by Castellani and Chalmers (Tropical Medicine 1929 p 2034)

Treatment.—As a rule the disease responds at once to a sulfonamide given by mouth. Prior to sulfonamides and penicillin these cases were extremely stubborn. Débridement by gentle measures is important with a view to avoidance of autoinoculation. An antiseptic such as Aureomycin or Terramycin ointment may then be applied Bichloride of mercury 1 10,000 in wet applications is excellent. Scratching and picking at the lesions must be prohibited. Penicillin injections, along with permanganate baths, are efficient when sulfonamides are inadvisable

STREPTOCOCCIC DERMATOSES

Included are streptococcic impetiginization subacute and chronic impetigo intertrigo (some cases) streptococcic fissures streptococcic epidermitis pityriasis streptogène seborrheic eczema (some cases)

Symptoms.—The streptococcus can cause persistent scaling and oozing inflammations which tend to undergo fissuring and which are painful and stubborn in response to treatment, especially wherever folds or flexures are involved (Chipman ADS 4 526 1921) Other streptococcic diseases, impetigo ecthyma erysipelas scarlet fever streptococcic gangrene and fissure of the lip are described elsewhere.

Impetiginization may follow impetigo or it may develop as streptococcic infection superimposed on and secondary to dermatitis of various causes. Banal irritation or comparatively inconsequential dermatitis venenata is occasionally so infected, particularly when it is located in a fold or flexure where the skin is moist All stages of dermatitis are seen, ranging from crusted, oozing areas to dry scaly patches. Fissures are especially common behind the ears (spectacle frames and perspiration abet this) at the angles of the mouth and at the anterior angle of the naris. Fissure of the lip (q v) is usually streptococcic

Pityriasis Streptogène, the chronic, dry type is seen usually on the face in the form of furfuraceous patches, practically asymptomatic except the branny desquamation. Behind the ears the dermatitis is likely to present a red and weepy surface glazed and covered with exudation. Dry scaling may involve the ear canal (Williams et al. J 113 641 1939) The whole scalp

and neck may be affected in widespread cases. Circinate, furfuraceous patches of the face in Negroes, producing depigmentation, were called erythema streptogenes by Dobes and Jones (ADS 53 107 1946)

Etiology—While hemolytic streptococci are often found in impetigo nonhemolytic organisms are the ones found in streptococcic intertrigo (Kinnear BMJ 1 291 1935 BJD 48 173 1936 Mitchell ADS 19 659 1929 40 635 1939 J 104 1220 1935 108 361 1937 Barber: Lancet 2 35 1935) It is wise to make smears, cultures and antibiotic sensitivity tests in cases of exudative dermatitis, for the findings affect one's choice of therapy

Prognosis and Treatment.—The duration of these disorders may be prolonged. They are resistant to treatment by ill-chosen or irritating measures. Weak ammoniated mercurial paste (2%) removed with benzine and refreshed twice a day may help Sabouraud used 1% iodine in alcohol Débridement gently performed is essential to success. X ray therapy has only a little value in temporarily diminishing the swelling redness and pain. All involved regions must be treated at the same time for a nostril will not heal if an infected postauricular area is neglected In cases affecting the corners of the mouth the teeth must be freed from calculus, decays repaired, pyorrhea adequately dealt with and dead and abscessed teeth removed. In streptococcic acrodermatitis Mitchell found correct diagnosis the fundamental requirement distinguishing fungous infections and dermatitis venenata and utilizing weak bichloride of mercury soaks and ammoniated mercurial ointment in cases in which streptococci are identified Focal infection must be sought out and eradicated. Sulfonamides by mouth not topically are highly efficacious in streptococcic diseases and so usually is penicillin by injection Many cases however represent mixed infections and topical therapy is also desirable using for example Chloromycetin, 250 mg in an ounce of Vioform Cream or an ointment containing tetracycline neomycin or dihydrostreptomycin. Gentian violet is not useful against streptococci. Injections of dihydrostreptomycin sometimes do a job that penicillin has failed to do

ERYSIPELAS

Symptoms.— St. Anthony's fire is an acute polymorphonuclear cellulitis due to streptococci when they involve skin and subcutaneous tissue. It is characterized by redness, edema and induration, accompanied by intoxication. Cutaneous manifestations are generally preceded by feelings of malaise and chilliness followed by fever The dermatitis begins as a small erythematous patch which gradually enlarges, the involved skin becoming swollen and indurated pinkish or reddish hot and tender with a glazed surface on which bullae occasionally develop Margins of the patch are sharply defined from the first, and lesions usually spread gradually by peripheral extension. Local symptoms are seldom severe but there are some burning and itching Lesions are generally single and seldom involve very extensive areas. Two or more discontinuous regions of activity may be seen in rare cases. The extent and rate of spread are measures of the severity of the disease. In infections of little virulence and slow rate of spread the central zone may clear as the periphery slowly expands. The face is a site of predilection, although no region is exempt There may be considerable swelling and edema particularly in cases involving the face and ears. The mucous membranes sometimes are attacked Occasionally a case is seen in which the inflammatory process is confined almost exclusively to the subcutaneous tissue, edema of the overlying skin being the sole superficial manifestation.

An attack uninfluenced by treatment generally lasts from one to several weeks, and fever is usually present throughout the course Within a few days or a fortnight the process reaches its acme then persists unchanged for a time and finally begins gradually to subside As involution takes place the dusky red color slowly fades to a brownish and then a yellowish hue and ultimately the epidermis regains its normal color There is always more or less desquamation.

Etiology.—Spink and Keefer (JClinInv 15: 17 1 1936) in a study of 30 cases found β hemolytic streptococci in the lesions or in the nasal secretion of all cases. *Streptococcus pyogenes* produces (1) streptococcic hemolysin (2) streptococcic leukocidin (3) an erythrogenic toxin (4) a fibrinolysin and (5) a substance which increases skin permeability and these aggressive substances somehow determine its pathogenicity. Perhaps antitoxic immunity which is the essential factor in resistance to scarlet fever is relatively ineffective as a protection against *Str. pyogenes* invasion of the skin the essential feature of erysipelas. While the erythrotoxin may play a part in the disease it seems that the degree of antitoxic immunity which will protect against scarlet fever will not protect against erysipelas.

Erysipelas like lesions occurring in acute nephrosis (q.v.) were remarked by Aldrich and Boyle (AmJDisChild 50: 1050 1939). Acute edematous cellulitis starts in an area of some 3 to 3 cm. diameter and spread very rapidly migrating especially to the dependent parts. The edges are not raised. The lower half of the body is affected. Favorable response was obtained with large doses of convalescent serum from patients who had recovered from erysipelas or scarlet fever.

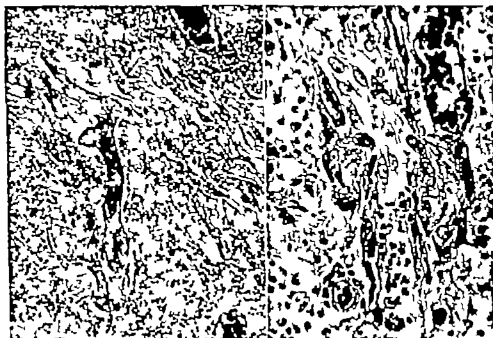


Fig. 303.—Erysipelas, showing polymorphonuclear and plasma cell infiltrate throughout dermis, and swelling of sweat duct. (Dr. Fred Weidman.)

Fig. 304.—Erysipelas showing capillary congestion, swelling of sweat duct epithelium, and polymorphonuclear leukocytic infiltration. (Dr. Fred Weidman.)

Pathology.—There is fibrinous and leukocytic exudation throughout the dermis. Blood and lymph vessels are dilated and congested. There is marked perivascular infiltration consisting mainly of polymorphonuclear leukocytes. The prickle cells are swollen, cloudy and vacuolated. Colliquation necrosis is usual. Streptococci are found chiefly in the lymphatics but are also distributed in the tissues. The inflammation, violent as it is, usually resorbs completely with no cicatricial sequelae but recurrent attacks, while comprising a rare clinical picture, can provoke chronic fibrosis and elephantiasis.

Prognosis.—In 1,193 cases (Hoyne: MRec 141 132 1935) the mortality was highest in the first year of life (39%) and in old age (43% in the 76- to 85-year group). The pregnant patient developing erysipelas is likely to abort within 24 hours (Lynch ADS 26 997 1932). One should note the dates of the studies quoted for sulfonamides and antibiotics have profoundly influenced the prognosis: erysipelas is no longer a disease to be dreaded and in fact, curiously I do not see many cases nowadays.

Acute glomerulonephritis is a possible sequel (see p. 28?).

Mortality rates arranged according to age groups and treatment methods were given by Nelson et al. (J 11 : 1044 1939): on sulfonamide, 1.6% of adults and 18% per

cent of children died; on antitoxin 9.2% of adults and 8.5% of children died; on serum ultraviolet, x ray and topical therapy 7.1% of adults and 10.7% of children died. The mortality rate was 16% in 1400 hospitalized patients reviewed by Keefer and Spink (JClinInv 15: 17 1, 1936). The rate was high in the first two years of life, low until age 60, then rose rapidly. Bacteremia was of grave import as was coincidental debilitating disease also.

Fatal cases according to Toomey (AnnIntM 12: 166, 1938) occurred generally among (1) infants less than 1 year of age, ( ) patients more than 50 years of age, (3) patients with pulmonary disease such as tuberculosis and pneumonia, (4) patients with chronic organic disease such as myocarditis and arteriosclerotic disease, (5) patients with concomitant acute infections, (6) patients who had a severe debilitating illness immediately before their erysipelas, (7) patients with alcoholism and (8) patients who had suffered severe injury. Not all patients in these groups died, but all of Toomey's patients who died belonged in one of these.

In 369 cases seen in Panama (Miller et al.: SMJ 38: 757, 1945) 46 were primary and 2.5% died. Whites were 4 to 5 times as susceptible as natives. In addition to local lesions, other manifestations in order of incidence were chills, local lymphadenitis, vomiting, headache, aching, anorexia, pharyngitis, diarrhea, convulsions, icterus, distention, delirium, toxic psychosis and orbital abscess.

Diagnosis.—Erysipelas is to be distinguished especially from erythematous contact dermatitis. The marginated, indurated lesions perhaps with bullae but not with eczematous vesiculation are distinctive, and the patient with erysipelas has fever and leukocytosis, and is sick. Compare Lupus erythematosus, systemic.

Treatment.—Morphine may be used freely. Good nursing care used to be of great importance. Bed rest, the urging of fluids, and alkaline diuretics are usually ordered. It has become common knowledge (J 108: 32, 1937) that sulfonamides possess remarkable properties in the cure of streptococcic infection and in minimizing its complications.

With their use, lesions of erysipelas become dusky red and purplish within the first 1 to 4 hours and disappear completely within 4 to 10 days. Inflammation resolves, symptoms improve and fever falls almost at once. One should institute treatment early. Sulfanilamide reduced hospitalization time from 11 to 7 days in the experience of Nelson et al. (J 11 1044, 1939). It reduced mortality rates as compared with antitoxin from 9.2% to 1.6 in adults and from 37.5% to 1.9 in children. Treatment other than sulfonamide was adjudged obsolete by Shank et al. (J 117: 2235, 1941) in whose experience no lesion spread after 36 hours of chemotherapy while only 10% of the patients were febrile after 4 days. One may give both penicillin and sulfadiazine.

A dose of from 100 to 300 r of unfiltered x ray therapy may be given over the affected area and a margin of 2 inches of surrounding normal skin as early in the course of the disease as possible followed by the same dose the next day (Bormann: DWchr 100: 131, 1935).

Ultraviolet ray treatment of the lesion and a surrounding zone of uninflamed skin was said to have value. 20 times the erythema dose was advised by Titus (BritJPhysM 9: 160, 1934). Ultraviolet therapy was highly recommended by Nightingale and Starr (J 102: 761, 1934) and Lavender and Goldman (J 105: 401, 1935). It diminished mortality in infants by 20% as compared with antiserum therapy (Starr: APhysTher 18: 772, 1937). It was the best method of treatment at that time according to Knapp (APhysTher 16: 711, 1935; 18: 872, 1937).

Antistreptococcic serum has been proved beneficial and should be given a trial in extremely toxic cases (Eley: AmJDisChild 39: 529, 1930; Foot: SouthMJ 23: 29, 1930). No local medicament reaches the subepithelial region of activity. Continuous cool packs are more or less comforting, the solution being inconsequential if it is nonirritating. Ichthyol ointment is popular but inert.

SULFONAMIDES.—See Domagk (DMedWchr 61: 250, 1935) prontosil; Colebrook and Kenny (Lancet 1: 1279, 1936); Foulis and Barr (BMJ 1: 445, 1937); Snodgrass and Anderson (BMJ 2: 101, 1144, 1937); Long and Bliss (J 108: 32, 1937; SouthMJ 30: 4 9, 1937).

Recurrent Erysipelas.—Relapse may occur within a few hours or days after apparently complete dissipation of the disease or after months or years, Andrews noted (Diseases of the Skin, Saunders, 1954). Antistreptococcic therapy should not be discontinued too early.

Chronic recurrent erysipelas constitutes a characteristic entity resulting in persistent lymphedema and elephantiasis. This rebellious and disfiguring disease to be distinguished from the erysipelas-like dermatophytid (q.v.) may respond to elimination of foci of infection and immunization with streptococcus toxin (Stevens: J 100: 1754, 1933). Andrews recommended also penicillin, plastic surgery and x ray therapy. Penicillin, x ray and solid

CO_2 did not help a case of Ormsby's (ADS 57: 403, 1948) O'Leary discussing this patient, advised a search for portals of entry of infection, the use of rubber bandages, vaccines or sulfonamides prophylactically and perhaps the injection of boiling water into the edematous area, which results in severe reaction occlusion of lymph vessels, and decrease in edema. Corticosteroid therapy is also sometimes beneficial (Andrews)

MELKERSSON'S SYNDROME, an elephantiasic swelling of the face associated with peripheral facial palsy was the name under which Kettel (AOtol 46: 341 1947) described 5 cases occurring in young men and women. The chronic swelling is sometimes bilateral. The onset of cutaneous changes often coincides with an attack of Bell's palsy but facial swelling may not begin until some years after the nerve palsy It is sometimes limited to the upper lip. The chronic recalcitrant edema may be concerned with hypothetical trophic fibers accompanying the seventh cranial nerve. Furrowed tongue is usually also present.

See QMN (J 139 193 1949) Machacek (ADS 61: 912, 1950); Stevens (J 156 323 1954) Hamilton (SouthMJ 47: 778, 1954) comparing erysipelatoid dermatophytid



Fig. 105.—Recurrent erysipelas producing chronic lymphedema. (Dr H C. Baum.)

SCARLET FEVER

Symptoms.—Scarlet fever is an acute febrile streptococcic infection usually of the throat, characterized by a toxic rash which is diffuse, brightly erythematous and productive of desquamation. The incubation period as a rule is short. Headache anorexia and vomiting are frequent early symptoms. High fever and a sore throat, which may present simple inflammation, follicular tonsillitis or a white diphtheroid membrane are typically abrupt in onset. Regional lymphadenitis is painful, and suppuration is not a rare complication. The throat is at first dry but later becomes congested raw and exceedingly tender The buccal mucosa may exhibit punctate redness, similar to that of the skin. The tongue is at first furred but later desquamates and assumes a peculiar strawberry appearance particularly at the border

The eruption at first diffuse and punctiform generally appears on the second day of the disease The neck and chest are usually involved first although the rash rapidly spreads to other parts of the body Only the circumoral region is ordinarily exempt. The eruption when fully developed at the end of the third or fourth day consists of closely aggregated, pinhead-sized or larger reddish macules which give to the skin a distinctly scarlet color Redness disappears on pressure and when the skin is stroked, transient white streaks are formed. Petechiae when present indicate grave intoxication, which may be such that death occurs within a few hours after the onset of the disease In mild and abortive cases the eruption may be slight or even lacking As a rule flaky desquamation commences between the seventh and tenth days and continues for a fortnight. Volar surfaces exfoliate slowly and sheets may come away in the form of casts of the affected parts. Nails are sometimes lost temporarily but hair is seldom shed.

Scarlatiniform eruptions may occur in streptococcic infections of the throat, surgical wounds, burns, *or pelvic and postpartum infections.* These may be considered true scarlet fever which is simply streptococcic infection with a symptomatic rash. Strains of streptococci differ in erythrogenic power and rashes occurred in from 47 to 0% of those infected with various organisms studied by Hamburger et al. (J 124 664, 1944) The rash of scarlet fever accompanied a streptococcic ulcer of the thigh in an old man with pneumonia seen by Kirby and Rantz (AIntM 71 620 1943) cure was obtained with sulfonamide therapy

THE DICK TEST consists in the intradermal injection of toxin; lacking antitoxin the susceptible subject responds with erythema while absence of response indicates relative immunity. Negative reactors got tonsillitis but no rash but Dick positives got scarlet fever as reported by Schwentker et al. (AmJHyg 38: 1943) See Dick and Dick (J 82: 265 1924; Scarlet Fever Year Book Pub., 1938) Rantz et al. (NEngJM 235: 39 1946) however, denied the existence of a relation between the Dick reaction and immunity to infection by hemolytic streptococci.

THE SCHULTZ-CHARLTON REACTION is seen when scarlet fever antitoxin or convalescent serum is injected intradermally into an area bright red with the rash of scarlatina. Blanching *occurs because the streptococcus toxin is neutralized.*





Fig 406.—Postscarlatinal desquamation (Drs Welsh and Schamberg.)
Fig 407.—Postscarlatinal desquamation (Dr Howard Fox.)

Diagnosis.—In drug rashes the history and the usual absence of fever angina and other signs of infection serve as *distinguishing features* atropine however can cause a scarlatiniform rash accompanied by fever and delirium Measles is characterized by its longer period of incubation, the primary involvement of the forehead and face the larger size crescentic arrangement and darker color of its edematous macules and the catarrhal involvement of the respiratory tract.

Treatment.—Prophylactic doses of toxin given to induce active immunity are likely to be followed by fairly severe reactions which may be avoided by giving 7 graduated doses at weekly intervals (Glazier NEngJM 233 204 1945) Nevertheless persons exposed to the disease occupationally should be protected (Anderson and Reinhardt JInfectDis 617 126 1935) *Convalescent serum* given to contacts early seems to abort the disease and even if given later seems to yield symptomatic benefit (Hoyne et al. J 105 783 1935) Human serum provokes no untoward symptoms. During an epidemic, it is

advisable to give sulfonamides to everyone likely to be exposed a gram a day of sulfadiazine brought one epidemic to an end (Watson et al. J 122 730 1943)

Sulfonamides given early in the disease are curative or else reduce markedly the incidence of complications (Sako et al. J 111 995 1938) but cannot be relied upon to the exclusion of other measures (French JHyg 39 581 1945)

Penicillin is probably more efficient for no complications occurred in 118 patients treated with it by Breese et al (AmJMedSci 211 417 1946) High dosage for 8 days is to be preferred, and this tends to reduce the carrier rate Orally 100 000 units q 4 h is effective (Hirsh et al J 133 657 1947) See Pulver (Der Scharlach und Seine Behandlung Huber 1954)

Reporting success with penicillin in 116 cases, Horne and Brown (J 133: 661 1947) adjudged it superior to sulfonamides and as good as convalescent serum. While inadequate doses may relieve symptoms dramatically high dosage is required to eliminate organism completely stated Jennings and DeLamater (AmJMed * 1, 1947) Sore throat subsided in ... days and fever within 4.5 days, as compared with 7 days when using sulfonamides, and the average duration of hospitalization was only 6 days in 1,000 cases reported by Jersild (Lancet 1: 671 1948) Of 56 patients with scarlatinal otitis, only 2 required mastoidectomy an operation which otologists are forgetting how to perform.

Convalescent serum, gamma globulin or antitoxin may do for the severely toxic patient what bactericidal medication cannot do (Fox and Gordon: AIntM 74 1 1944) In the series of Landon and Greenfield (AmJDisChild 76: 280 1948) there were 3½ times as many complications among those treated with penicillin as among those treated with gamma globulin and 5 times as many complications in those treated with convalescent serum. Yet gamma globulin was not highly effective, as penicillin was, in clearing the throat of streptococci.

One may presume it advisable to use gamma globulin, penicillin and sulfonamides together and cases should be recognized and placed under treatment early

Complications and risks are primary toxemia, suppurative cervical nodes, osteitis, especially of the mastoid, middle ear damage, nephritis and arthritis (Edit.: BMJ . 915, 194 ; Hamilton and Togasaki: JPed 14 655, 1939) Streptococcic meningitis occurred in only 19 of over 17,000 cases studied by Gordon and Top (JPed 6 770 1935) but killed 18 of the sufferers, whose purulent leptomeningitis came from the middle ear in 13 instances, from the sinuses in 4 and from the joints in 2. Gangrene of a leg can result from arterial embolism or thrombosis; while rare gangrenous complications were fatal in half of the 16 cases collected by Dick et al. (AmJDisChild 47: 374 1934); See Breen (Lancet 2: 196, 1940)

Topical therapy comforting to the patient includes an ice bag about the neck, cool moist applications such as aluminum acetate 1 500 and mineral oil during the desquamative stage.

RECALCITRANT PUSTULAR ERUPTIONS OF THE EXTREMITIES

One may well follow Andrews (Diseases of the Skin, Saunders, 1954) in the description of this group which includes forms which have so many characteristics in common that it is difficult to divide them definitely into separate entities. Dermatitis repens acrodermatitis perstans and pustular bacterid are diagnoses which excite discussion in any dermatological meeting I use the name dermatitis repens for rare cases of a particular clinical picture where soggy undermining of the epidermis is associated with local parasitism acrodermatitis perstans is put with chronic dermatitis of hands and feet (q v) and not used as a specific diagnosis and pustular psoriasis is applied strictly to clear-cut cases of psoriasis (q v) in which pustulation is present, perhaps as the result of focal infection, such as would occur if recalcitrant pustular acrodermatitis and psoriasis coexisted.

Pustular Bacterid implies that bacterial allergy can cause vesiculopustular lesions analogous with dermatophytids, a concept of dubious acceptability (Sulzberger and Baer YBD 148 p 21) The difficulties involved in using the name are avoided by calling such cases recalcitrant pustular acrodermatitis, which was defined adequately and aptly by Andrews.

Dermatitis Repens *usually follows an injury* small sore or paronychia. It is characterized by progressive and rebellious serous undermining of the epidermis with the formation of numerous minute abscesses. It begins with localized redness and vesiculation or pustulation. The central portion soon



Figs. 208 and 209.—Pustula bacterid. (Dr George C Andrews.)

consists of glazed denuded dermis, and this is surrounded by a ragged border of undermined epidermis. Serum and pus can be squeezed from beneath this marginal collar which ranges from 0 1 to 1 0 cm in width. There is little pain or itching. *The disease spreads slowly usually remaining unilateral. Staph.*

aureus generally can be isolated I look upon the disease as a chronic localized form of infectious eczematoid dermatitis (q v) generally responsive to elimination of foci, toxoid immunization and appropriate antibiotics. The combined parasitism and bacteria can produce the picture *Ps aeruginosa* seemed causative in 2 cases of Post and Hopper (ADS 63 220 1951)

See Barber and Eyre (BJD 39: 485, 1927) Dore (BJD 40: 12, 1928); Barber (BJD 42 500, 1930, 45: 113, 1933) Dore Barber and others (BJD 54 72, 91, 1942); Sachs and Scannone (JID 6 249 1945) Sachs et al. (ADS 56 748, 1947) Sachs, Andrews and others (ADS 65: 101, 1952) Bloom and Loriaux (ADS 70 819 1954) response to balsam of Peru; Murrell and Murrell (SouthMJ 48: 88, 1955) response to Terramycin by mouth, débridement and bacitracin ointment.

Pustular Psoriasis of the Extremities of Barber (see BJD 54 72, 91 1942) is generally bilateral and symmetrical and cultures are usually sterile. Circumscribed lesions of thenar eminences or soles are typical within which occur crops of minute intraepidermal pustules followed by drying crusting exfoliation and recurrence While some of such cases have been cured by elimination of foci, others have seemed incurable. Discussions of the confusing status of various clinically distinguishable manifestations of vesicular and pustular eruptions of the extremities by Dore and by Goldsmith (BJD 54: 72, 91 1942) are interesting My present interpretation of these cases invokes infection secondary infection focal infection, contactant irritation malnutrition, and metabolic imbalances in various combinations and degrees of causative consequentiality

Recalcitrant Pustular Acrodermatitis.—Andrews et al. (ADS 29: 548 1934) reviewed the features of persistent acrodermatitis, early lesions of which are intraepidermal pustules, which by confluence give rise to visible pustules and by peripheral spread produce crusted patches. They emphasized these uniform features of the varying clinical cases (1) failure of bacteriologic and mycologic examination to reveal organisms (2) unresponsiveness to all forms of local treatment including x ray therapy (3) coexistence of foci of infection (4) therapeutic benefit when these foci are eradicated (5) absence of features of psoriasis, with the pustular variety of which these cases have been confused Pustular bacterid includes cases in which the only cure rests on removal of foci of infection. Foci of particular importance are the teeth where pyorrhea and decay as well as abscesses are significant, tonsils, sinuses, kidneys, pelvic organs, vagina, and prostate.

Paronychial disease of this type is described separately by Andrews. A chronic and recurrently active vesiculopustular dermatitis of the terminal phalanges undermines the nails deforming them to a greater or lesser degree. Elimination of foci and contactants, along with penicillin injections, often proves curative. See Chronic dermatitis of the hands.

Etiology—Staphylococci and streptococci have both been found. Any inflammatory lesion such as a traumatic one acts as a filter for whatever circulating organisms may originate from a focal infection (Menkin Dynamics of Inflammation, Macmillan, 1940) See Andrews and Machacek (ADS 32 837 1935); Andrews and Barnes (SouthMJ 34 1260 1941)

Diagnosis.—Infectious eczematoid dermatitis mycotic infections, pustular psoriasis and primary micrococcic lesions of the extremities must be differentiated. Chronicity and rebelliousness to treatment are typical features. In infectious eczematoid dermatitis the eruption is usually of wide distribution and the patches are superficial. Fungi are absent.

Prognosis.—The disease may persist for months or years. A common sequel is x ray injury Response to proper treatment may be gratifying

Treatment.—Of local applications, soaks or poultices with 1:5 000 potassium permanganate may be helpful and I often prescribe 2% sulfur with 1% hydrocortisone in Vioform Cream One must eradicate foci of infection, eliminate contact irritants, and simultaneously attack with suitable chemotherapy



Fig. 310.—Recalcitrant acrodermatitis, psoriasiform.





Fig. 311.—Recalcitrant acrodermatitis. The same streptococcus was cultivated from paronychia and oral focal infection.

Fig. 312.—Dermatitis repens, affecting medial aspect of foot.

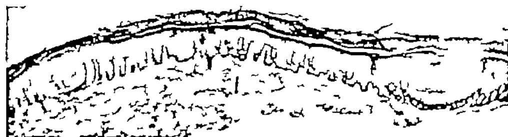


Fig. 313.—Pustular bacterid, showing superficial location of abscesses. (Dr. George C. Andrews.)

any parasites locally present. When the lower extremity is affected due attention must be given to circulatory problems, effort being directed at obtaining optimum conditions of blood flow. Measures corrective of anemia, hypoproteinemia, hormonal imbalance and defective liver function may be helpful. X-ray therapy offers nothing. Large doses of penicillin may yield benefit, likely to be only temporary, and this is true also of the sulfonamides (Sulzberger, ADS 40 843 1019 1939; Lever, ADS 49 273 1944). Immunization with staphylococcus toxoid can be tried. Cases are sometimes well palliated with cortisone, but elimination of foci is the essential measure.

GANGRENOUS DERMATITIS DUE TO INFECTION

Diseases in which considerable necrosis of the skin is a conspicuous feature may be caused by agents working locally or systemically. Gangrenous lesions are described under Bedsore, Burns and Frostbites, Anaphylaxis, Factitious Dermatitis, Occlusive Vascular Disease, Embolism and Thrombosis, Raynaud's Phenomenon, Rickettsial Infections (typhus), Syphilis, Leprosy, Noma, Cancer and Lymphoblastoma; see also Vascular Gangrene and Symptomatic Gangrene.

LOCAL INFECTIONS WITH GANGRENOUS DERMATITIS

Hemolytic Streptococcic Gangrene.—Meleney (ASurg 9 317 1924) pointed out that there is usually an initial lesion, which may be an injury or an operative procedure. Alarming rapidity of spread, swelling, stiffness, pain, fever and prostration characterize the early stages. The skin is first tense, smooth and shiny, but soon portions gradually turn darker, changing from red to purple, then to blue. Bullae may form. By the fourth or fifth day the purple areas become frankly gangrenous. A line of demarcation appears, the dead skin separates and beneath it is revealed extensive necrosis of the subcutaneous tissue. Sometimes the area of skin necrosis is small and subcutaneous loss extensive. Healing comes about slowly by granulation. In severe cases the process continues to advance until several large areas of skin have become gangrenous, the patient becomes more intoxicated, metastatic abscesses may develop and death ensues. The regional lymphatics are relatively little affected. Blood cultures in many cases show a microaerophilic hemolytic streptococcus, as do cultures from the lesions. The synergistic action of streptococci and staphylococci has been indicated by production of the disease in animals.

In treating undermining ulcers zinc peroxide has been recommended. It must be properly prepared to be of service (Meleney and Harvey, AnnSurg 110 1067 1939), mixed with equal parts of sterile water and applied everywhere to the surface of the infected tissue. The dressing must be a daily one carefully done, for direct and moist contact is essential.

Penicillin may halt the progress of the lesion, permitting spontaneous separation of the slough and rendering surgical attack unnecessary, while sulfonamides, strongly recommended a few years ago, have not been wholly successful in controlling the condition, according to Meleney et al. (Surg 18 423 1945). Many cases of chronic dermatitis with recalcitrant ulceration of the lower leg are associated with streptococcic infection and may respond to full doses of sulfonamides (Taylor, J 118 1196 1942). Antibiotic sensitivity tests may be expected to disclose an antibiotic which would cure.

Bacitracin seemed effective to Meleney et al. (AnnSurg 131 129 1950) but Meleney (J 149 1450 1952) was still finding a place for zinc peroxide which he recommended for synergistic gangrene only after excision, for foul ulcers especially cancerous, for diabetic gangrene, radiation burns and ulcerative colitis, and, as a prophylactic, around colostomies and in the sockets left by dental extractions. He thought well of it also in herpes zoster and poison ivy dermatitis. I do not share his enthusiasm.

Chronic Streptococcic Ulcers occur producing cutaneous gangrene which is slowly progressive and resistant to treatment (Goodman J 111 1427 1938) The undermined borders are irregular firm, thickened, ragged, and angry red in color The bases are roughly granular and glazed, discharging a copious serous fluid. Other than mild and transient lymphadenitis, there are no complications A symbiosis of streptococci and staphylococci was postulated as causative of geometric phagedena by Greenbaum (ADS 43 775 1941) See Dostrovsky and Sagher (ADS 54 408 1946) While penicillin by injection is highly effective, the 0 5% wet dressings of cysteine hydrochloride of Hamilton (OklaSMAJ 32 359 1939) deserve mention. Transfusions were highly recommended by Lyons (J 105 1972 1935) A buttock lesion which followed intramuscular injections of penicillin and streptomycin and required excision and grafting was reported by Wooldridge and Hogeboom (ADS 67 56 1953)

See Nixon (TexasSJM 33 216, 1937), 2 cases; Probstein and Helfets (JMoSMA 36 115 1939) infant Traub (ADS 38 94, 1938) correct preparation of zinc peroxide Hamilton (SouthMJ 31 440, 1938) pseudomycosis: injury pustulation, ulceration, brawny cellulitis, slowly spreading, punched-out ulcers, sinuses and undermining Wright and Friedman (ADS 39 554 1939) 3 year duration in old man, helped with sulfonamide Holman (BMJ 1 596, 1939), Lawrence (NEngJM 222 673 1940) cure with sulfonamide, Shallow et al (SGO 79 317, 1944) Marcus (BMJ 2 394 1950) 2 breast cases cured with streptomycin, Marcus (BMJ 1 1218, 1952, leg case requiring excision Ebbeson and Hardy (AnnSurg 123 1112, 1948) case following cold wave.

See also Leg Ulcers, Tropical Ulcers, Chancriform Pyoderma, and Pyoderma Gangrenosum.

Micrococcus mycetoma infections were described by Castellani (JTropM 36 249, 1933) who observed abrupt onset of a cellulitis suggestive of nocardiosis accompanied by fever ulceration and sinus formation, sometimes resulting in elephantiasic fibrotic changes. Similar lesions can be produced by *B typhosus* (Castellani JTropM 38 141 1935)

Progressive Postoperative Gangrene is a rare but clinically typical phenomenon of secondary infection of a surgical wound usually abdominal or thoracic. The lesion begins within 2 weeks as an erythematous induration at the edge of the wound. The inflammatory tumor becomes purplish or purpuric then undergoes central necrosis. Its progress may be extensive, and intoxication, fever and pain feature its course. Streptococci, staphylococci, or both as well as other organisms have been found. Treatment comprised radical excision at one time but one would expect penicillin and antitoxins to accomplish some cures (Touraine and Duperrat AnndeD 10: 237 1939 Dodd et al. ASurg 42 988 1941) Streptomycin by injection cured three cases in which sulfonamides and penicillin failed, according to Karn (NZealandMJ 48 380, 1949)

See Pilot (J 108 1694 1937) Carroll (AmJSurg 2 87 1938) Brodie and Bosch (CanadMAJ 42 133 1940) treatment with zinc peroxide and sulfonamides Lichenstein (ASurg 42 718 1941) Callam and Duff (BMJ 2 801 1941) anaerobic streptococcus and *B proteus* Behrend and Krouse (J 149 1122, 1952) fatal case

Gangrenous Balanitis (Phagedenic Balanitis) is a disease which develops rapidly and may give rise to deep and widespread gangrene The typical cases are apparently the genital manifestation of Vincent s disease for the spirochete and fusiform bacillus can be demonstrated, and the response to arsenical medication may be suggestively prompt. However synergistic coccic gangrene may affect prepucial tissue as well as tissues of the face or legs, the more common location of such lesions. Phagedenic ulcers of the genitalia are characterized by extensive and speedy destruction with comparatively little tissue reaction The slough is greenish gray The odor is putrid and offensive Fever and intoxication are likely to be great The regional lymph nodes are enlarged and tender Death may result. A copious, purulent hemorrhagic discharge characterized the case of v Haam (AmJTropM 18 595 1938)

Necrotic tissues should be cut away in such cases giving free drainage and access to chemicals. Oxidizing agents are used locally hydrogen perox

ide potassium permanganate or chlorine water soaks, or the actual injection into the tissues of oxygen gas. Appropriate antibiotics are of course indicated, and sulfonamides may be given by mouth.

Genital Ulceration in cancer tuberculosis, syphilis, actinomycosis, granuloma inguinale lymphogranuloma inguinale chancroid, paraphimosis, phagedena, gangrenous balanitis, ulcus vulvae acutum and Behçet's syndrome require differential diagnostic consideration (see Carlson JMoSMA 24 147 1937 Speiser AmJOG 43 681 1942 Leider USNMBull 41 278 1943) Biopsy smear culture dark field and intradermal and serologic tests are involved. Penile ulcers simulating chancroid but due to microaerophilic streptococci were seen frequently in southern Japan by Leibovitz (AmJSyph 38 203 1954)

See Campbell (SGO 34 780, 1922), 8 cases, 1 death; Whiting (AnnSurg 41: 841, 1905) 83 cases, 23 deaths; Hanschell (BJVD 20 123, 1944), mixed coccic infection cured with zinc peroxide; Reiter and Wentholt (JID 16 301 1950) primary fusospirochetal gangrene of penis, isolation of anaerobic pleuropneumonia like organism.



Fig. 314.—Gangrenous balanitis. (Dr F O. Harris)



Fig. 315.—Gangrenous balanitis. (Dr J E. Moore.)

Palpebral Gangrene in the Newborn.—Gangrene of the eyelids in infants is extremely rare but has been reported due to diphtheria, purulent ophthalmia and syphilis, and has been invariably progressive and fatal according to Pereira and Conti (ArchOftal 29 503 1954 abs J 157 1057 1955) Their patient, slightly premature and dystrophic developed a little red spot on the lower lid 10 days postnatal Rapid diffusion followed, with gangrene and penicillin was ineffectual. Death occurred after 12 days.

Granulomatous and Ulcerative Gangrene of the Face.—This is a rare, progressive destructive horribly disfiguring disease which has generally proved ultimately fatal Well described by Pardo-Castello et al. (SouthMJ 46 149 1953) it begins with necrotic ulcers in the skin and mucous membranes of the nose and mouth Granulomatous growths evolve and lesions spread to the skeleton of the face producing destructive osteomyelitis, ending in necrosis of the entire center of the face with frightful deformity of mouth nose, eyes and maxillae. The tongue and esophagus usually remain unaffected. The course has extended over a few months to years.

Malignant granuloma of the face was the title chosen by Levan (ADS 68 187 1953) who noted the slow onset and gradual enlargement of the granulomatous tumors. These may arise in the interior of the nose or on the palate and spread to adjacent structures, including the paranasal sinuses, posterior nasopharynx and soft parts of the midface. The patient retains good health until the terminal stages. Levan quoted the early reports of McBride (JLaryng 12 64, 1897) and Woods (BMJ 2: 65, 1921)

While the cause is unknown interesting speculations have evolved concerning the possible relation to systemic lupus erythematosus (Moore et al.: Laryngoscope 61 32 1951) and periarteritis nodosa (Stratton et al BMJ 1 1** 1953) The patient of Moore et al was a woman with rheumatoid arthritis of knees and ankles and erythematous lesions of elbows, hands and feet and cortisone induced healing while it was given. The patients of Stratton et al. showed a low-grade fever and developed albuminuria, renal and cardiac failure, rising blood urea, and necropsy changes of periarteritis nodosa in many organs. Dennie and Hamilton (ADS 4 : 1040 1940) thought *Spirochaeta microdentium* pathogenic in their case The patient of Cole et al. (ADS 43: 943 1941) was a congenital syphilitic and might have suffered ill effects from heavy metal therapy The patient of Astrachan (ADS 49: 7 1944) too, had received antisyphilitic therapy for years. Hargrove et al. (Lancet 2: 596, 1946) queried whether the disease might be sarcoma.

Zinc peroxide helped the patient of Costello (J 121 36 1943) Streptomycin, 3 Gm per day cured Williams (ADS 61 506 1950) Chloromycetin succeeded after penicillin and Aureomycin had failed in the patient of Sneedon and Colquhoun (BMJ 1 298 1952) Encouragement was afforded by the report of success with ACTH in the patient of Hagens et al. (AOtol 57 516 1953) who healed and has remained well (Hagens pers. comm 1955) Unexpected and unexplained cure followed a few small doses of x ray therapy in the case of Ellis (BMJ 1 1251 1955)

Systemic Infections With Gangrenous Dermatitis

Pyoderma Gangrenosum comprises a group of uncommon cases characterized by suppurative destruction of the skin associated with infection of long duration elsewhere in the body Brunsting et al. (ADS 22 655 1930) described 5 patients 4 of whom had ulcerative colitis and the fifth, thoracic empyema. Skin lesions include blebs, ulcers, pustules and abscesses, in which *Staphylococcus aureus* *S albus* and hemolytic *Str pyogenes* were found by Jankelson and Massell (AmJDigDis 3 19 1936) *B proteus* and *B pyocyaneus* may also be cultivated but it is difficult to know to what extent bacterial parasitism is directly responsible for cutaneous lesions.

Ulcers manifest slightly raised jagged, overhanging and undermined edges and bright red bases dotted with granulations and bathed in foul smelling yellowish green pus. They may attain a diameter of several centimeters.

In a review of cutaneous diseases associated with ulcerative colitis Sam tz and Greenberg (Gastroenterol 19 376 1951) noted 93 instances of skin complication in 65 (34%) of 189 cases. They observed oral aphthae and other forms of stomatitis, urticaria, erythema nodosum furunculosis and other lesio and 3 instances of pyoderma gangrenosum. The influence of deficiency with hypochromic anemia and hypoproteinemia, and the relation of skin manifestations to exacerbations accompanied by fever toxicity and purulent diarrhea have been stressed by various observers (Cohen ADS 33: 813, 1936; McClure: ActaDV 1 255 1940 Kiel ADS 56 187 1947)

See Schmidt (PBMMC 11 244 1936), Weiner (ADS 41 711 1940), F len (NYSJM 41 2228, 1941) Russell (BJD 62 114 1940) Brunsting (OhioMJ 30 1131 1934) review

The course of the disease is characteristically chronic Improvement and recrudescence in the internal chronic infectious process are respectively associated with evident trend toward healing and uncontrollable tendency to spread on the part of the skin lesions. At one time the patient may have scars, pustules and large integumentary defects, which may be healing or progressing The total number of ulcers ranges from 1 to a score or more and response to therapy is erratic Amyloidosis was present in the case of Bernstein and Goldberger (ADS 49 76 1944)

Vegetative pyoderma associated with ulcerative colitis is sometimes seen 5 cases difficult to distinguish from pemphigus vegetans were described by Brunsting and Underwood (ADS 60 161 1949)

The outcome is doubtful Some patients have become cachectic and died a majority however have passed through difficult periods with eventual return to health Much depends on the effectiveness of attempts to correct the underlying condition

Treatment.—Locally one may try Meleney's zinc peroxide paste (Brunsting ADS 41: 752, 1940) or sulfanilamide powder (Dostrovsky and Sagher ADS 48: 164, 1943). Wise (ADS 48: 551, 1943) used gramicidin ointment and administered sulfasuxidine, vitamin B complex and vitamin C with benefit.



Fig. 316.—Pyoderma gangrenosum in typhoid fever. (Dr G. B. Lemmon.)





Fig. 317.—Pyoderma gangrenosum. (Dr C. M. Stone.)
Fig. 318.—Pyoderma vegetans in axilla of a man with chronic ulcerative colitis. (Brunsting and Underwood ADS 60: 161, 1949.)

fit. Azulfidine, a favorite of Bargen, may be superior to other sulfonamide preparations. Ultraviolet light baths, transfusions, acetarsone by mouth, and various topical antiseptics have been recommended. The correction of inadequacies of nutrition, especially of protein, is a major effort but not easy. The

elimination of focal infection is necessary Antibiotics may or may not prove of much value those which may increase the irritability of the gut should be avoided or used with circumspection.

Gangrenous Dermatitis of Infants (Gangrenous Ecthyma) occurs generally as a rare complication of one of the exanthemata. Vesicular lesions becoming pustular develop into oval sloughs, which result in scars if recovery occurs. Trunk, buttocks and thighs are sites of predilection. A course of weeks o even months is marked by vomiting, chills, fever and intoxication. Such cases are likely to be in fact representative of *Ps. aeruginosa* infection (q.v.). Gangrene of the leg occurred in 2 cases a an embolic complication of scarlet fever (Blumenberger: AfKlinde halik 1936 p. 164). Hemolytic streptococci infecting varicella lesion caused extensive and fatal ulceration in a patient of Banks and McCartner (Lancet : 311 1937). Staphylococcus septicemia was the cause in a boy who wa treated with success by 25% urea wet pack (Blatt et al.: ADS 39: 407 1939). Enteritis preceded the hemorrhagic bullae which underwent gangrene in the two infants, brother and sister reported on by Urnela (abs ADS 39 395, 1939).

Dermatitis Nodularis Necrotica is characterized by a recurrent, polymorphous eruption of vesicles, papules, papulonecrotic lesions and ulcers preferring the back, dorsa of hand and feet knees, elbows and volar skin, with or without constitutional disturbance. Petechiae may occur. Scars and hemosiderin stains result. The hypothesis of tuberculous etiology has been discarded, while that of embolism seems plausible. Bacterial endocarditis brought to autopsy one patient of Duemling (ADS 1: 229 1930, 33: 99 1936) who found hemolytic streptococci in the skin lesions and lymph nodes of another. Reticulum cell sarcoma produced this picture in the report of Nieman and Wise (ADS 40: 560 1939) but Bernstein (NYSJM 40 ?7 1940) could not discover the cause in his 3 patients. Painless red lumps on the buttocks, legs and soles characterized the eruption which was present for 3 years following scarlet fever in a girl studied by Smith (BJD 61: 333, 1949).

A chronic nodular dermatosis, manifested by small, flesh-colored, painless lesions, was observed in a woman 48 years old by Bulter (Dermatologica 102: 139 1951). Minute pustules on the summits of some of the larger lesions yielded only *Staph. aureus*, and penicillin cured the disease although several courses were necessitated by relapses.

Compare Furuncles, globose lesions, p. 79

INTERTRIGO

Symptoms.—Intertrigo is a superficial dermatitis occurring on apposed surfaces characterized by redness, maceration and itching. Localized redness usually accompanied by hyperhidrosis, is the first manifestation. If neglected the skin becomes abraded and raw often with the formation of vesicles and pustules. The gluteal and crurocrotal folds, inframammary region and folds of the neck are common locations. In babies, napkin rash (q.v.) is the diagnosis often made.

Etiology.—Causative factors include friction, warmth perspiration and excretions supportive of floral growth. The usual parasites include the staphylococcus streptococcus, monilia and mycelial fungi, singly or in combination. Cultures from many cases showed in 10% of them pathogenic fungi (Howles AmJTropM 16 77 1936). *The disease is especially common in* obese persons and during the hot months. Leukorrhea urine and other discharges may be instrumental in its production, and diabetic patients are especially subject to the disease. Irritation of the skin by clothing soap or other toilet articles may render it vulnerable. Compare Streptococcic Dermatoses, and Moniliasis.

Treatment.—*In addition to keeping the parts clean the liberal use of a* powder such as zinc stearate or a mixture of zinc oxide and starch, is advisable. Ointments do not act well in these cases. Gentle sponging with a cool nonirritating antiseptic such as *1 10 000 bichloride of mercury or* 1:5 000 $KMnO_4$ is beneficial. The parts are dried by tapping with a soft towel and a bland powder is freely applied. Two per cent sulfur in Vioform Cream may be recommended. See Tulipan (J 116 1518 1941) on tannic acid and brilliant green in treatment. It is helpful to separate the affected parts by means of supportive brassiere or powdered pads. If there is oozing the areas may be painted with 2% aqueous gentian violet. Good ventilation

even an electric fan and drying radiant heat may be utilized along with aluminum acetate baths, half an ounce to 10 gallons of cool water Avoidance of contactants and elimination of focal infection may be necessary in the more difficult cases.

ERYSIPELOID

Erysipeloid is the infection caused by *Erysipelothrix rhusiopathiae* the bacillus of swine erysipelas, which generally reaches the human host through contact with an infected animal cadaver infecting not only butchers but also veterinarian students (Gross JKansMS 41 329 1940) This fine, rod-shaped nonmotile gram positive organism can be cultivated from the deep tissues of infected skin (Watts JPathBact 50: 355 1940) It may be seen in Gram stained sections in the deep capillaries of the dermis, accompanied by inflammation ranging from serous and edematous to leukocytic with or without suppuration, noted Klauder (ADS 50 151 1944) who described the diamond skin disease in hogs and discussed in human beings 3 forms (1) localized occurring at the site of occupational inoculation, exhibiting limited spread central clearing and the formation of marginate figures rarely vesicular often accompanied by periostitis and arthritis (2) diffuse and generalized, exhibiting sharply marginated, extending lesions which heal in older regions, repeated relapses but few or no subjective symptoms and (3) septicemic exhibiting septic fever sometimes endocarditis (Russell and Lamb J 114 1045 1940) with or without cutaneous manifestations which may comprise plaques curiously linear purpuric lesions located at creases and on palms and soles, or hematoma like swellings of the ears. Prolonged arthritis is a common sequel, often affecting wrists elbows, and shoulders (Klauder ADS 49 368 1944)

Treatment.—Solid carbon dioxide in less than vesiculating application relieves pain promptly is rarely required more than 3 times in 3 to 6 days, and cures localized infections in a week or so as a rule, according to Griswold and Bowen (ADS 49 348 1944) Sulfonamides have been used with fairly reliable success (Schoch and Shelmire ADS 41 570 1940) Immune serum may be preferable to sulfonamides and both may be given in resistant cases, stated Klauder and Rule (ADS 49 27 1944) The organism was shown to be penicillin-sensitive by Hellman and Herrell (PSMMC 19: 340 1944) and prompt and excellent results with penicillin by injection have been reported (Costello ADS 52 400 1945; Hodgson BMJ 1 483 1945 Ehrlich AIntM 78: 565 1946 Klauder and Rule JID 7 329 1946) Neomycin ointment topically and penicillin intramuscularly together yielded rapid cures in 90% of the cases reported by Gregory (MaineMAJ 44 1 1953)

The synergism of sulfonamide and penicillin was postulated following animal experiments by Klauder and Rule (JID 12 335 1949) The dose of penicillin must be adequate and may require repetition (Price and Bennett BMJ 2 1060 1951) Antibiotic sensitivity tests indicated effectiveness of penicillin, Aureomycin and Chloromycetin, in that order reported Sneath et al. (BMJ 2 1063 1951)

See Rosenbach (ZfHyg 63 343, 1909) original description; Klauder (DWchr 88 813, 1934) patient developing general disease committed suicide, was autopsied; Karlson and McNutt (JI (Dis 64 49 1939) microscopic aggl tination test; Morrill (JInfDis 65 322, 1939) student cases from horse cada er Greener (BJD 51 372, 1939) infection from peacock; Grinnan and Martin (ADS 41 1037 1940) generalized case with focus in gall bladder Ritchie (TexasSJM 38 226, 1942), case respon[illegible] to sulfonamide; Klauder et al. (J 122 938 1944) fatal case with egetati endocarditi Nicholas (ADS 54 47 1946) case followed crab bite, responded t penicillin Barber et al. (Lancet 1 128, 1946); Mac lay (WisMJ 45 1057 1946) Bush (BMJ 2 984 1949) case in veterinarian from dissection of turkeys; Dereda and Los (BMJ 2 1411 1949) June t October seasonal incidence notabl in British cases, which comprise bout 1 4 of "septic hands," lymphangitis being rare Good win (BMJ 1; 785 1950) Mc Dougall (Lancet 1 1348, 1951) Proctor and Richardson (Brit JIndustMed 11) 175, 1954) 253 Aberdeen cases mong fish workers, seasonal, few cases in cold months. Nelson (RockyMtMJ 52 40 1955) 500 cases among meat handlers, best results with penicillin.



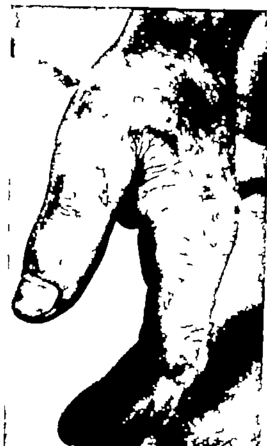


Fig. 319 —Erysipeloid, palmar lesion of 2 days' duration in battoir employee following puncture wound by a hog bone (Klauder J 111 1345, 1938.)

Fig. 320 —Erysipeloid, 8 days' duration, in battoir employee who cut thumb while work ing Note sharply defined, elevated border (Klauder J 111 1345, 1938.)





Fig 4 1 —Erysipeloid The stratum corneum stratum lucidum and stratum granulosum are normal Mild intercellula edema f the epithelium is present, nd there is slight dilation of the essels the papillary nd subpapillary lay rs. Cellular infilt t is most marked nea the essels (Dr Stuart C W y)

Fig 422.—Erysipeloid The cellular infiltration is haracteristically located deep l the dermis, pa ticularly in and round the f t cells (Dr Stuart C W y)

GONORRHEAL DERMATOSES

Gonorrheal dermatoses are cutaneous manifestations of infection with *Neisseria gonorrhoeae* either direct or metastatic.

Exanthems in acute gonorrhea include erythematous, papular and scarlatiniform rashes and rarely purpura. Annular erythema complicated a case of vulvovaginitis. Purpura and bullae with arthritis and a positive blood culture have been reported.

EXANTHEMA.—See Buschke (AfDuS 48: 181, 385, 1899 Wiedmann (DWchr 81: 541, 1934) bullous and purpuric exanthem Levin and Silvers (NYSJM 37: 1712, 1937) cutaneous eruptions; Kell (QJM 7: 1 1938) bacteremia with skin lesions, f ver arthritis.

Skin Lesions of primary gonococcal infection have been classed as (1) folliculitis, (2) ulcer a simple or serpiginous blenorrhagic chancre, (3) abscess, and (4) circinate balanitis by Kroll et al. (AmJSyph 28 320 1944) Their cases included a fluctuant abscess containing chocolate-colored pus on the shaft of the penis a pustular bleb near the frenum and a painless subcutaneous abscess in the foreskin.

Furunculoid lesions were noted by Lowry and Franks (AmJSyph 27: 4–8, 1943) A pustule with lymphangiitis developed in a laboratory worker accidentally inoculated with a pure culture (Sears: AmJSyph 31: 60 1947) Congenital fistulae of the median raphe were the locale in 4 cases of skin abscess reported by Mee (AmJSyph 33: 152, 1949) Primary cutaneous abscesses involved the dorsum of the penis in 3 cases of Scott and Thomson (AmJSyph 34: 262, 1950) and involved the coronal sulcus in that f Byers and Bradley (ADS 65: 503 1933)

Keratosis Blenorrhagica is a chronic inflammatory dermatosis, occurring in conjunction with gonorrheal infection of the genital tract and of the joints, characterized by a symmetric eruption of horny conical nodules, pustules and crusts on the palms and soles and other parts of the body It is practically invariably associated with multiple arthritic involvement The onset follows specific urethritis by several weeks or months. The disease is rare.

K ratosis blenorrhagica is evidence of grave systemic disease stated Ledany and Hughes (ADS 54: 150 1946) in a review of 165 cases. Its manifest tions are preceded by several days, weeks, or months by gonorrheal urethritis, prostatic and seminal vesicle infection being often present too. Arthritis nearly always ppears before skin lesions do. The exanthem is of sudden onset, associated with chills and fe e Its distribution is symmetric, with predilection for feet soles, ankles, and hands, and it ppears also about the arthritic joints and the genitals. It may be widely disseminated localized to the extremities. Typical les start as pinhead size or slightly larger vesicles firm, surrounded by rythema, becoming pustula with dry caseous contents. These ulcerate and develop dirty hard brown crusts with firm horny collars. Hemorrhagic blisters and erythematous patches may often be found in addition. In later stages there is extensive coalescence of mature lesions forming relief maplik areas perhaps affecti g an entire sole, palm, joint region. Such confluent areas have dusky red, slightly moist base, and sharp slightly raised margins, and are cov red with dry powdery scales, pe haps resembling psoriasis. Toes and fi gers show diffuse, slightly moist, rythematous involvement of the t rm nal phalanges on which tiny tense vesicles re scattered but these do not enlarge o pust late. This may resemble acrodermatitis perstans. Nails become dry and brittle and may be lifted from their bed by heaping up of subjacent horny material. The disease prefers men i the fourth decade who have had gonorrheal urethritis repeatedly Mortality has pproximated 10%. Neisserian organisms ha e bee demonstrated in perhaps 1 % of the cases.

Corneal ulcers complicated keratoderma in cases of Epstein and Chambers (ADS 36: 1044 1937) b t were successfully treated with artificial fever

Etiology—Barrett (ADS 22 627 1930) recorded 2 cases of keratoderma, in 1 of which the gonococcus was found in the vesicles, pustules and abscesses, but such a search has proved fruitless in the experience of many others. Gonorrhea is always present elsewhere however In a review of 83 cases, Downing (J 102 829 1934) noted that some have occurred in patients not having arthritis, and of the 5 reports of finding the organisms, only 1 seemed acceptable



Fig. 323—Gonorrheal abscess on shaft of penis. (Sobel ADS 45 [illegible], 1942.)

Fig. 324—Gonorrheal keratosis. ([illegible] ADS 9 423, 1924.)





Fig. 325.—Gonorrheal keratoderma; note arthritis of right knee. (Haase: JCutD 34: 817 1916.)

Fig. 326.—Gonorrheal keratosis. (Epstein: AmJSyph 21: 148 193[illegible].)

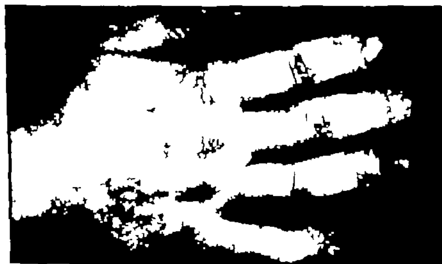


Fig. 327.—Gonorrheal keratosis.

When a moist, aseptic dressing was kept over areas of sound skin in a patient with keratoderma, pustules and keratoses developed under it (Photinos and Relias BSocfrançD 44 1775 1944)

Necropsies were reported by Simpson (J 60 607 1912), Lees and Percival (Lancet 2: 1116 1931) and Friedman (AmJPath 20: 09 1944) with interesting histologic studies. The earliest skin lesion is an abscess with polymorphonuclear leukocytes in the stratum granulosum, followed by dermal infiltration, papillary edema and superficial lymphocytic infiltration. The pustule widens and keratinization develops. A conical crust forms, and it may separate from intact skin beneath or new purulent inflammation may repeat itself under the crust so as to make a large, horny lesion. When death results, the cause is a combination of fever exhaustion and, likely bronchopneumonia.

A skin test i of immunologic interest in gonorrheal i fections. The filtrate of a bouillon culture injected intradermally induces a positive reaction, and reactivity disappears after the infection has been eliminated (Corbus JUrol 35: 11_ 1936) A 0.2 cm. reaction in 48 hours was seen by Conrad (NYSJM 36 1 67 1936), and there were no false positives. The test possesses diagnostic value and becomes negative when the patient is cured (Corbus and Corbus J 116: 113 1941)

Diagnosis—Pustular and arthropathic psoriasis are distinct entities (Epstein ADS 40 547 1939 BJD 51 428 1939 Blumenthal and Sherman Am JSyph 22 176 1938) Reiter's syndrome (q v) is to be distinguished but Ladany and Hughes believed some of these to be gonorrheal.





Fig. 328—Scalp lesions i gonorrheal keratoderma (Dr Harther L. K lm)
Fig 329—Keratosis gonorrhoica. (Dr Marcus Haase.)

Treatment—Elastoplast occlusive dressings and fever therapy were recommended by Taylor (BJD 51 418 1939) Hyperpyrexia has been accepted as effective since reports by Epstein (AmJSyph 21 148 1937) and later by Combes et al (J 114 2078 1940) Penicillin alone is sometimes curative (Emmet ADS 53 278 1946) but failure has been experienced Streptomycin was reported extremely effective a single injection of 0.3 Gm or more being curative (Chinn et al. AmJSyph 31 268 1947) Combs and Behrman (ADS 46 728 1942) *gave massive doses of vitamin A* and penicillin. (See Freireich et al AIntM 79 239 1947 Miale and Singletary ADS 57 151 1948) A case unresponsive to sulfonamides and penicillin was cured by streptomycin by Thompson et al. (ADS 59 284 1949)

ACTH was given with noteworthy benefit by Myerson and Katzenstein (J 149 838 1952) and cortisone in conjunction with penicillin yielded a prompt cure for Schwartz and Kingma (BJD 64 *388 1952) Streptomycin,* penicillin and ACTH together secured a 10-day cure for Shallard and Kanee (CanadMAJ 68 561 1953)

MENINGOCOCCIC DERMATOSES

Symptoms.—*Neisseria intracellularis* the meningococcus, is the infectious agent of epidemic meningitis which particularly in certain epidemics, is associated with petechial and purpuric lesions. If such a lesion of spotted fever is pinched pricked and squeezed and the droplet of blood and tissue juice is prepared with Giemsa, Wright or Gram stain diplococci may be found in perhaps 80% of the cases (McLean and Caffey: AmJDisChild 42: 1053 1931 Tompkins J 123 31 1943 Barnhard and Jordan JCLM 29 273, 1944) Conjunctival exudate herpetic fluid and the urine may likewise yield meningococci for early diagnosis (Sophian J 125 376 1944)

Herpes simplex, commonly of considerable severity accompanies meningococcus infection frequently Toxic erythemas and urticaria may be seen and serum sickness and dermatitis medicamentosa may appear in the meningitic patient

Acute catarrhal conjunctivitis often accompanies the infection and may comprise its sole manifestation (Theodore and Kost AOphth 31 245 1944) Purulent conjunctivitis resembled that caused by the pneumococcus in the case of Reid and Bronstein (J 124 703 1944) Hypopyon of one eye and a papular eruption on the legs were the first symptoms of meningococcemia in the girl reported by Kesteleyn et al (abs J 157 195 1955)

With regard to rashes in the acute disease distinctive is an irregularly round hemorrhage with a gunmetal-colored center composed of pus cells (Appelbaum AmJMSc 193 96 1937) The types of eruption emphasized by Costello (J 134: 518 1947) were (1) those resembling erythema nodosum, (2) petechial puncta interspersed with large hemorrhagic blotches, (3) lesions resembling flea bites with central hemorrhagic punctum and faint erythematous areola and (4) necrotic depressed lesions more or less simulating the papulonecrotic tuberculid. The earliest lesions are ill-defined erythematous macules in a dependent location by predilection, and the rash is multiform variable yet characteristic (Hill and Kinney J 134 513 1947) Petechiae favor the joint regions and pressure areas. The face palms, and soles are rarely affected. Lesions usually appear within 12 to 36 hours after the onset of disease, may develop in crops, and may fade in a few days irrespective of therapy

The rash may be sparse and hard to find. The commonest lesion is purpuric and from 1 to 15 mm. in diameter Sometimes there are only a few faint, pink, evanescent rose spots like those of typhoid Maculopapular lesions are usual, the larger ones being sometimes nodular or plaquelike tender and rarely quite large vesicular or even ulcerative (Daniels et al J 123 1 1943)

A skin test is of immunologic interest and vaccinal immunization can be accomplished. The whole culture produced vigorous skin reaction, the filtration produced less reaction and heating destroyed the capacity of the antigen to provoke any reaction, reported Kuhns (J 107 5 1936)

Chronic Meningococcemia occurs sometimes without meningitis. It may begin suddenly with fever pain in the joints, chilly sensations, and skin lesions. Suppurative arthritis is not found, but arthralgia is without effusion. Cutaneous manifestations appear in the first week and crops come out with each rise in temperature the lesions being various. A characteristic form is a rose-colored macule with a central vesicular pustular or petechial element (Ochs et al. BullUSAMD Sept., 1944) or small faint red macules or papules resembling erythema nodosum, or petechiae of small or considerable size may be seen An apparently insignificant rash is diagnostically as important as purpura, stated Hill and Lever (J 123 9 1943) Tender pea-sized, erythematous nodules appearing in crops were reported by Ingram (BJD 54 228 1942) in patients with positive blood cultures. In addition to macules papules, vesicles, and petechiae Mitchell Heggs (BJD 54 283 1942) described ulcers, sloughs and dermatomyositis.

Migratory arthritis and erythema nodosum may be due to meningococcemia a low grade infection simulating rheumatic fever but proving on

blood culture to be meningococcic (Stott and Copeman Lancet 1: 1116 1940 Copeman BMJ 1 283 1949)

Treatment.—Sulfonamides internally, perhaps given intravenously at first, are extremely efficient The organism is also sensitive to penicillin

Waterhouse-Friderichsen Syndrome.—Fulminating adre al hemorrhage, sometimes meningococcic in etiology and sometimes of unknown cause (see Purpura F lminans) is a catastrophic illness generally fatal, in which the abrupt onset with fever nausea, vague abdominal pains, headache and restlessness are soon followed by lilac cyanosis, shock and ge eralized petechial rash which spreads rapidly Peripheral circulatory failure ensues,



Figs. 330 and 331 —Meningococcemia. (Mitchell-Heggs BJD 54 263, 1942.)



Figs 33 and 333 —Meningococcemia (Dr G B. Mitchell Heggs.)

and the course rr s in from 8 to 24 hours. In 16 cases, the meningococcus was found in every one by Ferguson and Chapman (AmJPath 4: 763, 1948) who thought the deaths due to o rwhelming bacteremia a d to emia rathe tha to drenal destruct on. Pratt Thomas et al. (SouthMJ 38 229 1945) described 4 cases with 1 recovery due to sodium sulfadiazi e given intravenously Oxygen, drenal cortex extract and plasma were also helpful in a patient of Johnson (ADS 53 391 1945)

Cortisone ha changed the outlook remark bly for it rescues the patie t from shock, thereby making ailable the hours necessary fo the sulfonamides to eliminate bacteria (Nelson and Goldstein J 146 1193, 1951 Newman J 146 1229 1051) Alert diagnosis and prompt institut on of treatment are imperati e for cortisone and intravenous sodium sulfadiazi e are lifesaving

In spite of antibiotics ad these chemotherapeutic agents patie ts still die in shock. Treatment of early peripheral vascular collapse a major problem can succeed if Arterenol (norepinephrine) given ntra enously (Muhl NEngJM 49: 229 1953) The Water-

house-Friderichsen syndrome is not necessarily secondary to acute adrenocortical insufficiency; perhaps the ultimate cause of peripheral vascular collapse is extensive vascular damage with capillary hyaline thromboses, and continuous infusion of Arterenol to maintain a normal blood pressure may be a lifesaving measure (Weiner: J 153: 973, 1953)

TULAREMIA

Symptoms.—Tularemia is the disease caused by *Pasteurella tularensis* which commonly infects rabbits from which it is conveyed to man by inoculation usually at the site of a minor abrasion

About 3 to 4 days after infection illness begins suddenly with headache chilliness vomiting fever prostration and aching pains all over the body Such symptoms are readily mistaken for influenza The tularemic chancre when present usually occurs on the hand and develops slowly as a painful papule which soon sloughs, forming a soft flabby painful, punched-out ulcer Regional lymph nodes enlarge first becoming painful tender and centrally necrotic sometimes suppurating through the skin. Lymphadenitis may become general Illness and fever persist perhaps for 3 weeks, but convalescence is slow and is characterized by great weakness and disability which may continue for several months, unless treatment is given.

The ulceroglandular type is the common one but a primary sore is not always present In its absence the case is classed as typhoidal Tularemic pneumonia may develop in either Of 225 cases, among which occurred 17 deaths, 181 were ulceroglandular 7 were oculoglandular (the chancre being about the eye) 14 were typhoidal, and 23 simply glandular (Pullen and Stuart J 129 495 1945) The hands and fingers bore the primary sore in 175 cases. Subcutaneous lymphangiitic nodules were present in 18 cases, and these were firm movable nontender as a rule but attached to the skin and ulcerative in a few instances. Erythema nodosum like lesions were found in 6 cases. A diffuse papular rash occurred in 9 cases, appearing usually in the second or third week lasting usually only a few days. It was prominent on arms and neck was bilateral and symmetric, and included erythematous macules on the palms. Of the deaths, 12 were due to pneumonia and 1 to tularemic meningitis. Hitch and Smith (ADS 38 859 1938) described tularemic eruptions, noting the primary ulceration, which may be mucosal and the generalized rashes, in which macules papules, vesicles, and pustules have all been recorded

Many vectors are recognized, the vertebrates being listed by Burroughs et al. (JInfectDis 76 115, 1945) while insects are occasionally and ticks are often carriers (see PHRpts 55: 667 1940) The organism may be transmitted from animal to animal and from animal to man by wood ticks (epidemic reported by Dvil ld et al.: J 127: 191 1945) dog ticks, and deer flies. The pelts of infected animals also convey the infection. Tularemic infection of a tick does not harm it or its fecundity (Bell JInfectDis 76: 83 1945)

Pulmonary lesions observed by Archer et al. (J 104 895 1935) included pneumonia with *necrosis, pleuritis with effusion nodular and peribronchial* infiltrations, residual fibrosis and perhaps an increase of previous calcification Pericarditis was observed in 2 patients of Meredith (AnnIntM 32 688 1950) While streptomycin helped one of these, it did not prevent constrictive pericarditis, probably because it was given late Tularemia caused miscarriage in a woman who contracted the infection in the eighth month and the dead baby was infected (Lide AIPath 43 165 1947) See Lillie et al. (The Pathology of Tularemia Public Health Service Bull. 167 U.S. Treas. Dept. 1937) a 217 page monograph.

Diagnosis.—Tularemia must be differentiated from typhoid fever glanders, anthrax, actinomycosis, and sporotrichosis. Significantly high or rising titer of the agglutination test is diagnostic (Simpson OhioSMJ 29 35 1933) Positive blood cultures and animal inoculations of aspirated material may also be used in identification The opsonocytophagic reaction parallels the agglutination test and may help to distinguish brucellosis, which cross agglutinates with tularemia.

INTRADERMAL TEST —Foshay considered this to be as reliable as any skin test The few individuals who fail to develop positivity within a few days are persons over 51 years old as a rule Severe reaction occurs with vesiculation and necrosis if ordinary heat killed bacterial suspensions are used therefore Foshay used a test suspension made from virulent strains of *P tularensis*



Fig 334.—Tularemic chancre 19 days after its onset in a market man who dressed rabbits (Brown and Hunter in Stitt's Diagnosis and Treatment of Tropical Diseases, Blakiston's)





Fig. 335.—Tularemic chancre. (Dr Walter M. Simpson)

Fig 336 —Acneiform eruption in tularemia the arms were also involved (Dr Walter M. Simpson)



Fig. 337 —Primary lesion of tularemia, involving right index finger after repeated surgical incisions Nodular lymphangitis overlying metacarpophalangeal articulation. Photographed 6 weeks after onset. (Dr Walter M Simpson)

oxidized for , hours with nascent HNO and then adjusted to a turbidity equivalent to 100 parts per million of fuller's earth The test dose is 0 05 cc and the result is read at 48 hours. Foshay observed failures to respond as late as the sixth day never later There were no false positives. Reactivity remains positive, and the test will not distinguish present infection from ancient. The reaction resembles the positive tuberculin or brucellergin test

taking from 6 to 9 days to resolve and disappear. The skin test seemed highly specific during the first week, perhaps before the agglutination test becomes positive (Friedewald, AmJMSc 197: 493, 1939). Antigen for a skin test was made from necrotic lymph node material by Lawless (ADS 44: 147, 1941).

Prognosis.—Most patients recover fully but mortality ranges about 5%, the development of pneumonia being ominous. The mortality was 4% in 120 cases reported by Kavanaugh (AIntM 55: 61, 1935). The cause of death is septicemia and toxicity rather than pneumonia, believed Foshay (AIntM 60: 23, 1937), who noted that the third week is the dangerous one, most deaths occurring on the sixteenth day. Older patients cannot tolerate the disease as well as hardy young persons.

While it has been thought that no case has suffered reinoculation and that recrudescences were due to persistence of the organism, proof of reinfection was claimed in 2 cases by Green and Eigelsbach (AIntM 85: 777, 1950).



Fig. 331.—Tularemia. Sporotrichosis-like lymphangitis and lymphadenopathy. (Dr Walter M Simpson.)

Fig. 332.—Axillary adenopathy, massive and suppurating, occurring 3 weeks after onset in ulceroglandular tularemia. Spontaneous rupture occurred 2 days later. (Dr Walter M. Simpson.)

Prevention.—Hunters, vacationists, butchers, and housewives are especially exposed. A wild rabbit should never be handled with the bare hands. Infected meat is rendered safe by thorough cooking. The laboratorian working with *P. tularensis* is almost certain to become infected (Lake and Francis, PHRpts 37: 392, 1922).

A vaccine made by Foshay et al. (AmJPH 32: 1131, 1942) by oxidizing virulent strains of the organism with HNO_3 is promising in the prevention of the disease, but 7 persons who had received the vaccine became infected, according to Howe et al. (J 132: 195, 1946). Vaccination which provokes severe reaction in persons already possessing immunity reduces the incidence of laboratory infections by about two-thirds (Kadull et al., JImmunol 65: 425, 1950) and can be recommended to those who expect exposure as an occupational or recreational hazard (Edit., J 144: 1408, 1950).

The therapeutic effectiveness of streptomycin and Aureomycin, especially in cases diagnosed early, makes vaccination less imperative. Streptomycin cured the technician who contracted a tularemic tonsillar ulcer after aspirating a culture from a pipette, reported by Jordan and Downs (JKansMS 50: 390, 1949).

Treatment.—Strict bed rest is indicated for patients who are ill. Surgical interference is useless even dangerous. X ray therapy relieves pain of local lesions. I have seen the antiserum of Foshay (AmJMScl 187 235 1934) yield excellent results. The use of this serum plus neoarsphenamine was recommended by Werling (OklaSMAJ 35 103 1942) or *with 2% sodium bismuth* tartrate 1 cc per 100 pounds daily intravenously reported favorably in 61 cases by Jackson (AmJMSc 209 513 1945) Atabrine yielded results encouraging to Ecke and Ecke (IllMJ 93 318 1949) Penicillin was ineffective in cases of Josey (J 126 496 1944) but Chloromycetin promptly cured 6 patients of Parker et al. (J 143 7 1950)

Streptomycin was found effective in the disease under experimental conditions by Heilman (PSMMC 19 553 1944) *and its superiority to specific* antiserum was recognized by Foshay and Pasternack (J 130 393 1946) and Foshay (IndianaMA 41 207 1948) Streptomycin, 7 000 000 units in 10 days, cured a pneumonic patient in whom penicillin and sulfonamides had proved ineffective (Cohen and Lasser J 131 1126 1946) although sulfonamides have been reported helpful in the past Streptomycin therapy did not alter the immune response for agglutination titers rose as in untreated cases, according to Johnson et al. (AmJMSc 214 645 1947) The excellence of streptomycin is attested by many reports, such as those of Bost et al. (J 137 352, 1948) Burson and Harwell (AmJMSc 215 243 1948) and Corwin and Stubbs (J 149 343 1952) 1.0 to 1.25 Gm. per day, in divided doses each 3 or 4 hours, *to a total of from 5 to 7 Gm suffices, and improvement is conspic*uous within 48 hours.

Aureomycin appeared to do more good than streptomycin or Chloromycetin in experiments with mice and appeared as effective as streptomycin in 3 human patients reported Woodward et al (J 139 830 1949) There are numerous articles on the effectiveness of Aureomycin, which Long et al. (J 141 315 1949) adjudged the first choice see Ransmeier et al (AmJMed 7 *518 1949)*

GLANDERS

Symptoms.—Glanders is due to *Malleomyces mallei*. The infection acute o chron c is characterized by the occurrence of vesicular pustular and ulcerative lesions, long with s t m c symptoms. It a comparati el common disease of horses mules, and donkeys, but it is fortunately a rare d sease in man. The early symptoms are those of mil l sept cemia malaise ague joint pai *fever* of intermittent type and prostration. Profuse cat rrhal purulent nasal discharge is regularly present, particularly in acute cases.

I the cut form the man festation of systemic in olvement grad ally become more ma ked and the pat ent sinks nto a typhoidal state and generally dies. The cute cons mptoms re ried. In cases in which i fection ha occurred through the skin, the nitial lesion *may be* ca buncular *papule or vesicle* More or less induration is *present* however and uperficial sloughing common. Characterist lesions develop in 1 to 4 week a groups of small deep-seated, reddish o yell wish papules which sometimes become es la o bullous, b t whi h invari bl soo e o late f rm ulcers. These may coalesce giv ng rise to l rge, gangre ou areas. L mph node involvement results in the f rmat on of subcutaneous od les f rcy buds. These tumors re lik ly to perforate the overlying kin, *giving rise to foul* suppurating *ulcers*

In the chron c f rm the lesion re fewer i n mbe and less violent in characte Cata rhal symptom develop late if at all. The d sease may persist for months o years Abscesses and lcers are occasionall associated w th metastat c foci subcutaneous and muscular tissues, joi t and lungs.

Glanders occurs mainly in men whose occupations bring them in contact with horses (Hunter Lancet 1 316 1930 Burgess CanadMAJ 34 _39 1936 Mend l+o ; USAFMJ 1 781 1950) The rganism i highly pathogenic nd has caused death of several laboratory workers Strict isolat on is required. *Six cases occurring in laboratory research* wo kers were reco *ded by Howe and Miller (A nIntM 26 93 194) 5 of whom were* infected via the respirat ry tra t a judged by the presence of pulmonary lesions

Diagnosis.—The involvement of th nasal m cosa s the most characteristic feature Thi the k n a d lymphati ol ement and th usually typhoid-like constitut onal symp*toms* should p event co fusion. I trad rmal and compleme t fix tion test re ava lable

Prognosis.—Practically all cases have termi ted f tally

Treatment.—Mallei an endotoxin which correspond with vacci ha been tried with some degree f success. In addition, surgical measures are to be employed Serum and vaccine therapy are ot satisfactory Sulf diazine ma be recommended (Horne and

Miller: AnnI tnM 26: 93, 194) Success with the use of streptomycin has been reported (J 14 : 46, 1950) While all 18 cases that occurred in 1939-1948 in Turkey were f tal (all traced to contact with horses with farcy) a recovery I 1949 followed the use of streptomycin, penicillin and sulfa iiarl and in 1951 a ure was obtained with sulfadiazi alone and in 1953 with Aureomycin and streptomycl (Corresp. from Turkey: J 15 : 143, 1953)

MELIOIDOSIS

Melioidosis is a glanders-like disease which occurs primarily i rodents and also in man Stanton and Fletcher (JHyg 23: 268, 1924; Studies Inst. M. Res. F M S., 21, 1932) having collected 83 cases of human infection with the *Pfeifferella wh tmori (Acti o-bacillus pseudomallei)* Abscesses, pustules, and sinuses are found, although the important lesions are consolidations and abscesses of the lungs li e spleen, sometimes the kidneys. This septicopyemia in man usually is fatal within 3 or 4 weeks. Acute and chro ic forms are seen. In the acute cholera-like vomiting, collapse purgi g and death may occur in 72 hours. In chronic forms, multiple abscesses may develop in all organs except the brain particularly affecting the lu gs, spleen, and live Cutaneous vesicles a d pustules may simulat variola. The essential pathologic lesion is a small area of necrosis developing into an abscess, coalescing with ear by lesions of similar character and forming a honey comb containing creamy or i the liver glairy greenish pus (Edit: BMJ 1: 344 1947) A chronic case from the Western hemisphere was reported by McDowell and Varney (J 134 361, 1947) a d sulfonamides penicillin, and streptomycin were ineffectual; wide ca tery excision helped most. S lf diazine seemed helpful to Mirick et al. (J 130: 1063, 1946) Autoge ou vaccine was used by Peck and Zwanenb rg (BMJ 1: 337 1947) in a patient who did not die. Experimental i fections were not responsive to Aureomyc n (Cruickshank: BMJ 2: 410 1949)

See Whitmore (JHyg 13 1 1913), original description Covi re (Rev d'hyg 57 100 1935) 95 cases reported through 1932, 98% fatal Cox and Arbogast (AmJCP 15 567 1945) cute, fatal case with scattered pustules, palpable spleen and li er pulmonary abscesses Paton et l (BMJ 1 336 1947) f tal case w th pericard tis, effusi pleuritis, purpura.

BRUCELLOSIS

Brucellosis.—Three types of organisms belong to the Brucella group: *Br meli tensis* associated with undulant fever; *Br abortus*, more virulent for human beings than the others; and *Br suis*, perhaps the commonest in humans. A typhoid like roseola appears i about 5% of the cases (Simpson and Frazier: J 93: 1958 1929) An ulcer localized on the face (Michel Béchet, abs BMJ 1: 893 1940) and a case resembling dermatitis herpetiformis (Urbach: DZtschr 64: 230, 1932) have been described. Nodular scrofulous, chronic lesions of th face pai less and subcutaneous at first, late forming craterif rm ulcers and fistulae were seen in the Brazilian patient of Pacheco (abs YBD 1931 p. 89)

Skin Test.—Culture filtrate may be given intradermally as a diagnostic test. The *reaction usu lly ppears promptly showing wide erythema and central edema, which may* even slough along with constit tional symptoms. Reaction may be dela ed (Fla nerv: J 114 1234 1940) The test or repetition of it may be lon of co siderab e therapeut c value. Th test i negative unless the reaction persist for 7 to 10 days; it may persist much longe While the test depends on tissue sensitivity induced by the presence in the body f organisms f the Brucella group diagnosis wants substantiation by the presence of symptoms of the active disease (Ervin and Ho t J 109 1966 1937) The intradermal skin test is nevertheless the most reliable confirmation f a diagnosis of chronic brucellosis (Benning: J 130 320 1946)

Brucella Dermatitis.—Of 50 practicing veterinarians subjected to inquiry by Huddleson and J h son (J 94 1905 1930) 20 per cent admitted developing a rash on the arm when t was inserted into the vagina of cows which in thei opi ion w re infected with *Br abortus*. This manifestation of eczematous eactivity makes its ppearance in 20 min tes, and dependi g on the degree of sensitivity t is (1) light red and blotchy o red and unif rm, d it hy or burning but not edematous, persisting for 4 to 8 ho rs and disappearing w thout desquamatio ; or it is (2) papular the les ons bei g discrete and elev ted, not highly pruritic, lasting 3 4 days, a d hanging to a brown color before disappearing without exudat on or desquamation.

See Thomsen (ArDuS 163 477 1931) original description of llergic dermatitis on forearms of veterinarians Jadassohn (ArDuS 164 657 1931) patch tests.

SKIN TESTS.—Huddleson et l (AmJPH 23 917 1933) kin llergy and immunity Keller et al (J 107 1369, 1936 SouthMJ 31 1 1938) kin tests Gould and Huddleson (J 109 1971 1937), intradermal test with 0.1 cc suspensoid of 1 2,000 nucleoprotein best, read in 48 hours; Angle et l (AnnI M 12 495, 1938), skin test raised serum antibody titer; Gerab nd Black (APath 27 397 1939) histology f tuberculoid skin reaction to test Harris (J 131 1485, 1946) kin test negati in some acti ely infected patients, technic important, read after 96 hours Harris (J 142 161 1950) necrotic skin reactions from intra dermal testing cured by Aureomycin

TREATMENT OF BR CELLOSIS Tisdale and McCullough (J 135 1033, 1947) sulfadiazine and streptomycin Braude et al. (J 141 831 1949) Aureomyci effecti e; Herrell and Barber

(PHMMC 24 138, 1949) Aureomycin and dihydrostreptomycin; Spink et al. (J 138: 1145, 1948 139 352, 1949) Aureomycin best Herrell and Barber (J 144 519 1950) Aureomycin and dihydrostreptomycin with 1 symptomatic relapse in 35 patients.

CHANCROID

Symptoms.—Chancroid, or soft chancre is due to inoculation, usually venereal, with *Hemophilus ducreyi* which soon produces small, autoinoculable painful ulcers of relatively benign character usually located about the genitalia. The earliest manifestation, a minute reddish macule appears at the site of inoculation after an incubation period of 3 to 14 days. It quickly becomes an inflammatory pustule which ruptures and forms a small, shallow circumscribed ulcer The ulcerative lesions may become single through confluence of multiple early lesions although they may remain multiple As a rule they are circular or oval, with soft, nonindurated, slightly undermined edges, and grayish granular floors bathed in pus. A reddened areola is usually present, although there is but little induration except in chronic lesions. Chancroidal ulcers being autoinoculable spread by expansion, inoculation and coalescence The duration ranges from 10 days to several months. Giant and destructive ulcerative lesions are occasionally seen.

Extragenital sores are seen but are rarely primary A primary ulcer on the finger was noted by Brandt et al (VDI 22 89 1941) See Syphilis, mixed chancre (p 388)

The regional lymph nodes are infected and the resultant buboes may suppurate This involvement may be unilateral or bilateral. It is accompanied by pain and fever See Sullivan (AmJSyph 24 482 1940) monographic.

Etiology—*H ducreyi* is a small slender nonmotile nonspore-bearing non acid fast gram negative bacillus which generally forms chains. It can be grown with difficulty but the technic of Beeson and Heyman (AmJSyph 29 633 1945) enabled them to obtain diagnosis by cultures in three-fourths of their cases. There is evidence that the bacillus of chancroid sometimes exists in the female genital tract as a saprophyte In smears from the ulcer the organisms may be found as small ovoid rods arranged in pairs, groups or chains lying parallel to one another They may be intracellular or extracellular Human volunteers were successfully inoculated with pure cultures by Tomaszewski (ZtschrHyg 42 327 1903) The experimental disease in monkeys and rabbits was described by Reenstierna (ActaD-V 2 1 1921)

Qualitative chemical analysis of the organisms revealed nitrogenous constituents consisting of simple and degenerated proteins, amino acid derivatives and nucleoproteins polysaccharides and glucosides, which like the nucleoproteins, were specifically antigenic (Ronzani abs YBD 1939 p. 137)

Pathology—Superficial necrosis pervaded with polymorphonuclear leukocytes, and a peripheral zone rich in plasma cells lymphocytes, and perithelial and endothelial leukocytes characterize the lesion (Torpin and Dienst AmJSyph 22 634 1938)

Diagnosis.—In syphilitic chancre the period of incubation is long from 3 to 6 weeks the lesion is comparatively painless erosion but not ulceration is typical lymph node involvement is characteristic, the nodes being firmly elastic nutlike painless and freely movable and *Spirochaeta pallida* can usually be found in the lesion. Mucous patches of the genitalia are always accompanied by other evidence of syphilis. Cancer usually develops after the fourth decade of life chancroids before that period In cancer there is often a history of long-continued irritation and the lesions develop slowly and are always indurated

Biopsy yields specific diagnosis in some 90% of cases cultures in 75% smears in only 50% according to Heyman et al (J 129 835 1945) The skin test alone is inadequate Diagnosis by autoinoculation may be considered (Strakosch et al JID 6 95 1945)



Fig. 340.—Chancroid.



Fig. 341.—Chancroid. (Dr B. A. Kornblith.)



Fig. 342.—Penile chancroid and digital lesion due to autoinoculation. (Dr O. G. Costa.)





Fig. 343.—Chancroid, chronic and grossly deforming. (Dr Harold N Cole.)
Fig. 344.—Chancroid, 6 months duration. (Dr Harold N Cole.)

Mixed Infections.—In lesions caused by conjointly inoculated syphilis and chancroid prolonged observation is required to diagnose syphilitic infection. Dark field examinations help These should be performed on several successive days during which treatment is limited to saline dressings. Serologic tests for syphilis should be made monthly for 6 months (see J 116 2405 1941) Penicillin sufficient to cure early syphilis, 2 doses of 1,200 000 units each, may as well be given in doubtful cases.

Skin Test.—The vaccine may be used by intradermal injection as a specific diagnostic test the Ito-Reenstierna reaction (Saunders et al NYSJM 39 447 1939) Cole and Levin (J 105 2040 1935) found that sterile pus from the chancroidal bubo will serve in lieu of vaccine There is an interval of about 5 weeks from the appearance of the sore until the development of demonstrable skin allergy to the specific antigen Sensitization does not develop unless considerable regional lymphadenitis occurs (Dienst and Gilkerson AmJSyph 31 65 1947) A positive test may be obtained even 30 years after infection. Positive reaction means only a past or present infection.

Skin Test.—Ito (AfDuS 116 241 1913); Reenstierna (MunchMWchn 1920, p. 893 AfDuS 147 362, 1924), Frei (HandbHcwl 21 1 1937) Dulaney (AmJSyph 21 667 1937) Hunt (PSExpB 33 252, 1936), vaccine from pure culture for skin test, cultural methods Greenblatt and Sanderson (ADS 36 486 1937), preference for bacillary [illegible] Sanderson and Greenblatt (SouthMJ 30 147 1937) culture method of preparing [illegible] Dienst (AmJSyph 32 [illegible] 1948) antigen as good from avirulent as from virulent culture Willcox (AmJSyph 36 284 1952) question of transplacental transmission of skin reactivity

Prophylaxis.—A 10% aqueous solution of Zephiran chloride and a 2% solution in propylene glycol were 100% effective in preventing experimental inoculations if applied within one hour (Combs and Canizares ADS 51 237 1945) while mild mercurous chloride and 15% sulfathiazole emulsion were 85% effective if applied within 6 hours. Soap alone was not effective Penicillin yields no prophylactic effect but streptomycin does (Willcox AmJ Syph 34 378 1950) *Sulfathiazole Aureomycin and Chloromycetin* protected from heteroinoculation experimentally performed but penicillin was a poor prophylactic, and antimony bismuth and neoarsphenamine were ineffectual (Willcox ADS 62 533 1950 BJVD 26 131 1950 BMJ 1 509 1951)

Prognosis.—Chancroids heal readily as a rule Occasionally ulceration is extensive Complication with phagedenic coccic or Vincent's infection may lead to serious fulminating destruction. If the ulcer is excised or is adequately drained by circumcision before the bubo has developed the bubo fails to develop Modern treatment has simplified the disease so that it has become relatively trivial, and the sulfonamides have rendered surgical measures obsolescent (Kornblith et al. J 117 2150 1941)

Treatment.—Simple cleanliness is requisite Violent chemical measures are harmful rather than beneficial, although cauterization with nitric acid was a time-honored procedure If phimosis complicates, mild astringent applications such as 1 500 aqueous solution of aluminum acetate may be employed until the inflammation subsides.

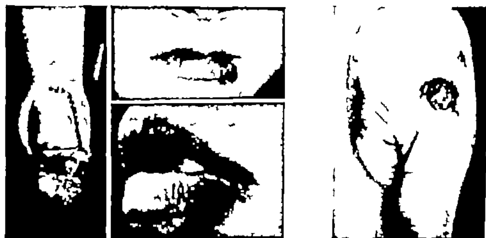
A popular presulfonamide method consisted in moist antiseptic soaks, alternated with drying, o[illegible] nde the influence of radiant heat and a dusting powder such as iodoform Beneficial soaks are hydrogen peroxide warm 1 5 000 potassium permanganate and 1 10,000 bichloride of mercury Specific vaccine treatment has been especially successful in chronic serpiginous ulcers. Injections were given intrav[illegible]ously at intervals of 3 days. The dose must be conservat[illegible]ve and fever was expected. Prior to sulfonamides, the bubo, if fluctuant wa[illegible] punctured, pushing the knife through normal ti[illegible]ue at the periph[illegible]ry The content was expressed an antiseptic injected, and a pressure bandage applied. Circumcision diminished the average hospital sta[illegible] by 4 days reported Rauschkolb (ADS 39 319 1939)

Sulfanilamide yields remarkably beneficial effects, a dose of 1 Gm each 6 hours being recommended. In the absence of bubo 21 Gm. of sulfathiazole in 5 days cures as efficiently as larger doses while in the presence of bubo 7 days of treatment do as well as 14 and experimental infections are cured in 3 days stated Combs et al. (AmJSyph 27 700 1943) Sulfonamides will not cure all phagedenic cases (Canizares and Cohen ADS 42 640 1940) Sulfanilamide powder may be applied locally and it may be packed into an

abscessed bubo when this is opened. Uncomplicated cases respond to bed rest and sulfathiazole 21 Gm in 5 days if simple, 29 Gm. in 7 days if bubo is present the drug being given 2 Gm. to start with and 1 Gm four times a day (Combes NYSJM 46 1700 1946) More is not necessary

The effectiveness of sulfonamide medication is attested by articles by Batchelor and Lees (BMJ 1: 1100 1938) by Hutchinson (Lancet 1: 1033, 1088) who found that sulfanilamide resulted in 15 days of hospital care in cases of bubo as compared with 42 days with surgery or with Dmelcos vaccine by Henschell (Lancet 1: 836 1938); Greenblatt and Sanderson (AmJSyph 23: 603, 1939); Schwartz and Freeman (J 114 946, 1940); by Culp (AmJSyph 4: 622 1940) who found buboes disappearing without incision; by Trautman and Emeshieer (abs VDI 23: 763, 1942); by Satulsky (J 127: 259 1945) who in 1,533 cases found dorsal slit needed in only 6 occasionally punctured a fluctuant node and injected 1 cc of 7% tincture of iodine and calculated average hospital stay at 11.2 days.

Antibiotic sensitivity tests on *H ducreyi* in vitro showed moderate sensitivity to streptomycin, *none to polymyxin and little to* penicillin bacitracin or Aureomycin (Wetherbee et al AmJSyph 33 462 1949) Penicillin is without value in chancroidal infection (Pereyra and Landy USNMBull 43 *189* 1944) *despite the fact that the organism is susceptible to penicillin in vitro* (Tung and Frazier AmJSyph 29 620 1945) *Streptomycin cures* chancroid in rabbits (Mortara et al *AmJSyph 31 20* 1947) and 15 human cases, proved by culture were cured by streptomycin by Hirsch and Taggart (JVDI 29 47 1948) Jawetz (ADS 57 916 1948) cured 15 cases *with 10 Gm given in 5 days.* Streptomycin cured *the sulfonamide-resistant* case of Weber et al (AmJSyph 33 58 1949) In *a dose of 2 Gm daily for* 5 days it cured 61 cases reported by Taggart et al. (AmJSyph 33 160 1949)



Figs. 346-347.—Granuloma pyogenicum, finger tip and lip cases.
Fig. 348.—Granuloma pyogenicum of left thena skin.





Figs. 349 and 350.—Granuloma pyogenicum of tooth socket and of tongue. (Dr. How rd Fox.)





Fig. 351.—Gran loma pyogenicum of immense size. (Drs. A. P. Biddle and A. C. Woltenberg.)
Fig. 352.—Gran loma pyogenicum ar lbow. (Dr. Sam. I. B eltzer.)

spread infiltration mainly of connective-tissue cells with a few leukocytes intermixed round cells plasma cells and mast cells. Clumps of staphylococci are scattered through the growth Gross section of a lesion widely excised shows its bulging elastic translucent whitish composition, arranged as a cone-shaped mass lying within the skin the apex at least as deep as the level of the sweat glands this explains the failure of clipping off at skin level as a method of treatment



Fig. 353.—Granuloma pyogenicum of chin, unusual lesion (Ayres ADS 69 331, 1949)



Fig. 354.—Granuloma pyogenicum, showing resemblance to hemangioma.

The lesions seem to bear the same relation to granulation tissue that keloid bears to cicatrix (Berger et al. APath 21 273 1936) and they are not related to botryomycosis.

Treatment.—The lesions are harmless but persistent Excision followed by cauterization is successful if adequately destructive Radiotherapy can be used (Eisen CanadMAJ 42 628 1940) the dose must be rather large comparable with the dosage used in treating keloid. I give 500 r once a week for from 3 to 6 doses. A cure was reported by injecting the base of a lesion with 300 000 units of penicillin dissolved in 1.5 cc. of procaine solution (Spilz inger abs J 151: 1456 1953)

See Hatzell (JCutDis 22 520, 1904) Wile (JCutDis 28: 662, 1910) Sutton (J 66 1012, 1916) Armstrong (ADS 2 128 1920) Hoffmann (HandbHuG 8 I 397 1929), Thoma (Clinical Pathology of the J ws, Thomas, 1934 p. 344) epuli gra ulomatosa Kelly (ADS 31 884 1935), lingual tonsil involved; Maury et al (BsocfrancD 46 493 1939) gia t case on leg ulcer Frank and Blahd (AOtol 31 919 1940) 5 nasal fossa cases; Allison (ADS 45 679 1942) upper lip case cured with sulfathiazol

Staphylococcic Actinophytosis (Botryomycosis) is a rarely recognized entity distinct from granuloma pyogenicum (Berger et al.: APath 1: *"3, 1936) The lesion is a small tumor containing a granular sanguinopurulent exudate within which are microscopic granules simulating those of actinomycosis. Crushed or cultured these bodies are found to be composed of masses of nonhemolytic but coagulase positive *Staph aureus* (Drake et al.: J 1-3: 330 1943) In at least 7 of the reported cases foreign bodies have been discovered in the lesions.





Fig 355 —Human bartonellosis, erupti stage Disseminated miliary nd nodula lesions of the f ce Palpebral conjuncti f the right ye with errugas. Most of the lesions were pink bright red The patient still show emaciation due t the preceding ttack of Oroya fever (Gradwohl et al Clinical Tropical Medicine, Mosby 1951)

Fig 356 —*Barton lla bacill formis* in the peripheral blood from case of Oroya fever (Hemsa stain (×1 480) (Photogr ph by C Sanma tin.) (Gradwohl et al Clinical Tropical Medici e, Mosby 1951)

VERRUGA PERUANA

Symptoms.—Verruga peruana (Peruvian warts Oroya fever Carrió s disease) is a disease e demi w th n certain inland portions of Peru due to infection with *Barton lla bacill formis.* It is characterized b fe e of a l termitte t remitte t or irregular type, followed o ccompanied by rapid and progressive anemia and the eruptio of pinhead t pea size red w rty inflammat ry tumors. The disease i limited in it geographical dis tribution to the region between lat tu les 8 and 13 S in Peru between altitudes of ,500 and 9,000 ft. on th west slope of the A des It e pecially likely to be contracted in hot ravines which are heltered from high wi d (Fox J 104 045 1035) Lactescent plants and the insects on them are n olved n its tran mi sio The sandfly transmits th d sease *Phlebot m rrucarum* be g the pri cipal spec es invol ed (Edit.: J 122 153, 1943) See Ed t, (J 113 35, 1939) and (lo l t (Hases d l control sol re la ve ruga, Lima, 194)

Benign an l mal gn t form of the disease re seen the malignant var ety bei g se re acute and prod ct ve of profound anemia.

The period of cubat on ranges from to 6 week o l ger a d i haracterized by fe e of rregul t pe jo t pa ns, heada h and ba k h nd a em a of se re grade On the ppeara ce of th erupt on these mptom graduall subside and may disappear Earl cut neous manifest tion re usually purely eryth matous The d s tribution is roughl mmetric a d more o less ge eral although the face neck, and

extensor surfaces of the arms and legs are the sites of predilection. The mucous membranes are early involved Within a few hours or days groups of papules many of which later become nodules, develop in the erythematous spot These lesions are of various sizes, from 0.5 to 4.0 cm in diameter, bright or dark red in color and sensitive to touch They may be sessile, cylindric or pedunculated. Their capsules are thin and fragile, and readily rupture giving rise to hemorrhages which tend further to debilitate the already weakened patient. In addition to surface lesions, nodular masses commonly develop in the subcutaneous regions, particularly about the joints. In time many of these break down *to form deep, foul ulcers, which are likely to give rise to hemorrhages of greater or less* severity Some superficial warty growths may shrivel up and disappear, and many larger ones undergo absorption but the course of the disease may be prolonged over a period of many months by the development of new groups or crops of lesions, each outbreak usually being preceded by recrudescence of fever and anemia.

Etiology—Barton's bacillus is found in the local lesions, as well as in the red blood cells during the febrile period of the disease These small, pleomorphic, motile aerobic, Gram negative organisms, 0.2 to 0.5 μ by 0.3 to 1.5 μ, dumbbell shaped and coccoid, occur singly and in masses.

Diagnosis.—The symptoms are suggestive and the eruption is pathognomonic. The agglutinin titer is maximum just prior to the appearance of the eruption when positive blood cultures may be obtained (Howe: AIntM 72: 147 429 1943)

Prognosis.—The mortality averages about 15% Sluggish cases may drag along for months, and the patient finally recovers while in those with hyperpyrexia, severe anemia and great prostration death may occur within a few days. One attack yields lasting immunity

Treatment.—Change of climate particularly removal to the seashore, often proves beneficial. Treatment prior to the advent of antibiotics was largely symptomatic, though arsphenamine has been thought to be sometimes helpful. Howe (1943) tried hyperimmune rabbit serum in 3 cases, but results were not dramatic. Streptomycin appears to be curative (Aldana et al.: ArchDerm J 139: 605, 1949), while penicillin and Chloromycetin do not affect the course of the eruption, although they induced disappearance of Bartonella from the peripheral blood (Krumdieck: ArchDerm J 143: 1 19 1951)

Prevention is readily accomplished: it consists in staying away from infected regions and in avoiding them particularly at night DDT affords promise in control efforts.

RHINOSCLEROMA

Symptoms.—Rhinoscleroma is a chronic granulomatous disease which affects the nose and upper respiratory tract. Women are attacked more commonly than men Persons who live in poorer hygienic conditions appear to be more susceptible The first stage is characterized by rhinitis, fetid nasal secretion and dryness of the throat the second stage by localization of the infiltration, obstruction of the nose and damage to the larynx and the third stage by nodule formation and heavy invasion (Reyes ADS 54 531 1946) *A fourth stage of cicatricial evolution was added by Kline and Brody* (ADS 59 606 1949) who spoke of the symptoms as being largely mechanical and preferred the name Scleroma

The disease begins insidiously with nasal symptoms comprising at first crusts and foul discharge then obstruction and epistaxis. Diffusely or discretely there develop hard, insensitive cartilaginoid plaques which are subcutaneous and later extend superficially (Cunning and Guerry AOtol 36: 662 194) The overlying skin gradually assumes a peculiar reddish or brownish glistening hue and may become scaly and crusted. Within several months or years, the tumors tend to grow irregular or lobulated, with smooth or slightly wrinkled telangiectatic surfaces, and they are firmly embedded in the skin.

Ultimately the masses diminish in size and become dense and hard. The resulting deformity depends on the location and extent of involvement. The disorder generally affects the anterior nares, upper lip and contiguous structures, but cases have been reported in which the pharynx, larynx, trachea, tongue and even the lacrimal passages and the lobe of the ear were involved, either primarily or secondarily In the nasal cases the nostrils are thickened and stiffened, and the tip of the nose is enlarged and elevated. Infiltration may be so great as to close the area entirely Mobility of the lips may be impaired so as to interfere with speech. The mucosa of the nose and pharynx becomes puckered and shrunken. The gums are involved in rare instances, and the teeth become loose and may fall out. Ulceration is rare but may occur as a result of accidental injury or infection. The course of the disease is extremely tedious, extending perhaps over a period of many years. There is lymphadenopathy.

Etiology and Pathology—It is possible that rhinoscleroma is due to a short, encapsulated, gram-negative bacillus isolated by von Frisch (1882) which is morphologically almost identical with the pneumococcus of Friedländer although the results of animal inoculation experiments have been negative There is little evidence to show that the organism of v Frisch is primarily responsible for rhinoscleroma. There is no means by







Fig. 357 —Rhinoscleroma (Novy and Tauscig ADS 39 1058, 1939)
Figs. 358 and 359 —Rhinoscleroma. (Dr W S Gottheil.)



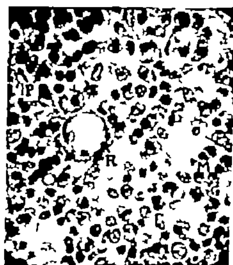


Fig. 360.—Rhinoscleroma (Dr Robert Andrade)

Fig. 361 —Rhinoscleroma. *M* Mikulicz cell *R* Russell body which is a plasma cell showing eosinophilic hyaline degeneration *P* plasma cells. (Dr Stuart C. Way)

which it can be distinguished with certainty from other members of the encapsulated group, which are found in healthy noses (Topley and Wilson: Principles of Bacteriology 1937). Nonpathogenic to mice. 10 strains investigated by Morris and Julianelle (J Infect Dis 55: 150 1934) absorbed agglutinins identically with type C Friedländer bacilli.

The tumor mass consists mainly of plasma cells, collections of which are irregularly scattered in all layers of the skin and subcutaneous tissue. The collagenous tissue is thickened and increased at many points in the tumor and it is this unyielding, fibrous material which accounts for the pathognomonic hardness of rhinoscleroma. Large, oval, dropsical cells first described by Mikulicz, and hyaline degenerated cells of Pellizari (Russell bodies) are characteristic regressive changes. Mikulicz's cells are probably degenerated plasma cells, each containing 0 to 8 of v. Frisch organisms. The hyaline degenerated cells are spherical in shape and, like the dropsical cells, are 4 or 5 times as great in diameter as the surrounding plasma cells.

Diagnosis.—The characteristic location of the lesions, their hardness, and the absence of ulceration are suggestive. Syphilis, carcinoma, other granulomas and keloid are to be excluded by biopsy.

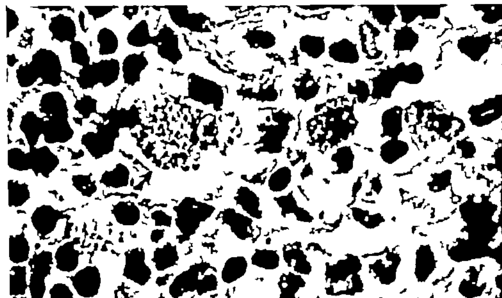


Fig 182.—Rhinoscleroma. Granulomatous tissue, showing Mikulicz cell designated by arrows. (Simpson and Ellis, ADS 39 681 1939.)

Prognosis and Treatment.—The disease is steadily progressive and remarkably resistant to treatment. Surgical interference is usually followed by recurrence. Radiotherapy given early has proved palliative. A case was cured by streptomycin, 250 mg each 3 hours to a total of 97 Gm. given because the Klebsiella group of organisms have been shown by Heilman (PSMMC 20 33 1945) to be sensitive to this agent (Devine et al PSMMC 22 597 1947). Streptomycin induced marked improvement within 5 days, during which cultures became negative, and recurrence did not take place in a period of 3 years in a patient of Russell et al. (J 148 642, 1952)

See Ireland (CanadMAJ 34 149 1936); Chamberlin (AOtol 23 285, 1936); Alderson (ADS 36 1012, 1937) Novy (ADS 39 1058, 1939) Gadomski (AOtol 29 681 1939) Quevedo (AnnOtol 58 612, 1949) 102 cases in Guatemala. New et al. (AnnOtol 57 416, 1948) streptomycin cure. Levine and Hoyt (AOtol 47 438, 1948) diagnosis.

ANTHRAX INFECTION OF THE SKIN

Symptoms.—Anthrax infection in the skin is manifested in a circumscribed, carbuncle-like inflammatory lesion due to *Bacillus anthracis*. Anthrax in man may be septicemic or localized. The septicemic form generally is a result of spread from local infection of the skin. The infection may be immediate from a domestic animal or its hide or hair (shaving brushes, J 117 115 1941) or mediate through the bites of fleas, flies, and other insects. The

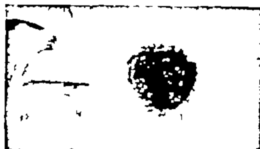




Fig. 363.—Anthrax. Tense vesicles around black ulcer. (Dr. Herman Gold.)

Fig. 364.—Anthrax pustule on neck, no longer edematous after treatment with specific antiserum, showing now only collar of vesicles about central ulcer. (Gold: J.Lab.Clin.M. 21: 134, 1935.)



Fig. 365.—Anthrax pustule on knuckle on fifth day of infection. (Dr. Herman Gold.)



Fig. 366.—Anthrax involving proximal aspects of forearm near elbow in a veterinarian.

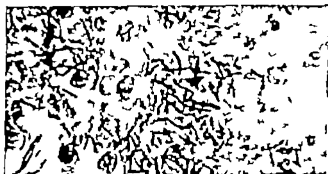


Fig. 367.—Anthrax bacilli in tissue. (Dr. Arthur St. Clair Brumbaugh.)

period of incubation ranges from 1 to 3 days. A small, pruritic reddish macule resembling a flea bite develops, to be followed in the course of from 12 to 24 hours by a red indurated papule which soon becomes vesicular or pustular. The lesion often contains blood and soon ruptures leaving a dark red base which dries and blackens within a few days. The sore is then a typical eschar surrounded by a vesicular zone. The disease may proceed to recovery or satellite vesicles may develop. The lesions are not necessarily of *the textbook description. It may resemble a smallpox vaccination or a streptococcic or staphylococcic sore and it may or may not show vesiculation* or eschar (Enrich BMJ 2 50 1933). Multiple lesions are uncommon.

Etiology and Diagnosis.—*B anthracis* may be found on apparently healthy animals. It causes disease in animals however as well as in man. Anthrax is an occupational disease among handlers of hides. Microscopic examination of smears suffices for diagnosis. *B anthracis* is easy to cultivate (Lebowich et al AmJClPath 13: 505 1943). The disease has been acquired in the laboratory by accidental inoculation (Soltys JlPathBact 60 253 1948). At least 30 such cases have been reported (Sulkin and Pike AmJPubH 41 769 1951) but only 1 of them was fatal. Wool and hair used in the carpet industry may harbor the parasite (Lloyd AIndustHyg 6 421 1952). Bone meal imported for fertilizer from the Far East has been the source of infection in a number of cases in Great Britain (Davies and Harvey Lancet 2 880 1953 Jamieson and Green Lancet 1 560 1954). An insect bite may have inoculated the patient of Hunt and Cook (BMJ 1 87 1955).

Treatment.—While early and radical excision of the lesions was at one time advocated expectant treatment combined with specific serum gave better results (Hodgson Lancet 1 811 1941 Gold AnnIntM 70 785 1942). Immobilization, as in the treatment of carbuncle, is an important measure. Antianthrax serum can be obtained from the Bureau of Animal Husbandry at Washington, D C., and it should be administered repeatedly until edema begins to subside. Sulfonamides have some value (Bonnar BMJ 1 389 1940) but *penicillin is now known to be paramount (Murphy et al. J 126 948* 1944 Ellingson et al J 131 1105 1946) rendering other efforts, excepting isolation unnecessary. The organism is also sensitive to streptomycin (Holgate and Holman BMJ 2 575 1949) and Aureomycin which protected guinea pigs from inoculation and cured 2 cases of Sanchez (MedMex 29 211 1949). Aureomycin was considered as effective as penicillin by Gold (AmJMed 8 31 1950). Chloromycetin and Terramycin are likewise curative reported Gold and Bogar (NEngJM 244 391 1951). Chloromycetin was entirely satisfactory in 4 cases of Clarke (BMJ 1 86 1952). Streptomycin and neomycin are also effective antibiotics, according to the in vitro tests of Boger (ADS 67: 541 1953). Recovery from anthrax meningitis followed the use of antianthrax serum sulfadiazine by mouth and penicillin by injection in the case of Kindler (IndustM&S 21 487 1952). See Gold (AIntM 96 387 1955).

See Para-anthrax. Leo Smythe and Bricker (JIndustHyg 4 53, 1922) 123 cases in Pennsylvania in leather industry 1916-1921 mortality exceeding 31% cut ½ by hospital care, rest, immobilization. Regan and Regan (AmJMSci 167 388, 1924) antiserum given locally round lesion also I M and I V avoid surgery, 14 cures, 2 deaths. Pinkerton (J 112 1148, 1939) horse t 55 miles to rancher who pelted them. Wyatt and Epstein (VetMJ 40 101 1941) 3 cases from dead cattle, cured with antiserum and sulfonamide. Lockwood and Gilderslee (J 116 1606 1941) neoarsphenamine and "hands off". Bendeman and Wheeler (J 135 837, 1947), case ivory worker from elephant tusk, fatal. Weinstein and Colliver (AmPract 2: 332, 1948) 3 cures with penicillin. LaRocetta (AmJMSci 216 407 1948) 36 cures with penicillin; Harasha and Lovett (AmJOphth 32 106, 1949) ocular. Griffin et al. (NYStJM 48 1718, 1948) 17 carpet factory workers 3 with meningitis, all cured with penicillin, some supplemented with sulfonamide. Cole (BMJ 1 1124 1951), 61 cases in Dar-es-Salaam, penicillin superior to sulfonamide. Wolff and Heimann (AmJHyg 53 80, 1951) industrial control measures. Wilson et al (JFlaMA 39 404, 1952) case in cowhand, review. Beaton and Strange (BritJExpPath 35 144, 1954) effective antigen for immunization from cultures.

DIPHTHERIA OF THE SKIN

Cutaneous Infection With *Corynebacterium diphtheriae*.—This may result from autoinoculation contact with an infected individual, or the use of contaminated articles. Cross infection of 16 of 18 patients on a ward was re

ported by Tauber and Goldman (ADS 4: 757 1942) Nasopharyngeal carriers are usually the source.

The eruption often comprises gray sloughing ulcerating patches which *develop around a swollen* inflamed wound. In many instances foci have been multiple and polymorphous, eczematoid or pustular in character Genital lesions are not rare especially in girls. Penile infection leads to sloughing *sores of the glans* (Crowther BMJ 2 646 1943) Umbilical infection in the newborn was reviewed with a collection of 66 cases by Thompson (BJChildDis 36 171 1939) Dermal lesions are usually ulcerative but may resemble impetigo intertrigo or varicella When impetigo is associated with conjunctivitis, diphtheria must be suspected for toxemia is not marked as a rule (Rogers IrishJMSc 150 283 1938) Impetiginous, purpuric pyodermic and ulcerative lesions in several instances accompanying diphtheritic conjunctivitis, were studied by Williams (BMJ 2 416 1943) who demonstrated virulence of the organisms in 12 of the 16 cases so tested.



Fig. 268—Pseudomembranous diphtheria of ankle seen 6 days after a minor injury (Gill ADS 49 408, 1944)
Fig. 269—Pseudomembranous diphtheritic ulcer of 7 days' duration. (Dr S. Gill)
Figs. 270A and 270B—Chronic diphtheritic ulcers of 10 months' duration (Dr S. Gill)

Diphtheria of the Lips was seen in 46 British prisoners of war in the Far East by Biddell (BMJ 818 1950) The pearly white or slightly yellowish, raised, glistening membrane was firmly adherent and covered usually the outer third of the upper and lower lips on both sides. The clinical appearance was quite distinctive Toxemia was generally insignificant After serum was given, the membrane separated within 48 hours.

Ulcerative Lesions occurring in Palestine were intensively studied by Gill (ADS 49: 408 1944 51 43, 1945) Occurring usually on the legs the sores may be solitary or multiple They follow insect bites or minor trauma. A serosanguineous pustule may develop with a wide areola, pain and regional lymphadenopathy Or a pseudomembrane appears, beneath which necrosis and sloughing produce a punched-out ulcer This loses its painful character in some 6 weeks, and cases are seen in which diphtheria is justly suspected as the original cause but only cocci can be found. Or proliferation of tender tissue follows rupture of the pustule and a deep central cavity without membrane formation ensues Erythema and pigmentation along with anesthesia about the ulcer are typical.

Multiple indolent ulcers, jungle sores in Indian troops were followed by weakness of the extremities loss of reflexes, blurring of vision and paresthesias (Ward and Mc... BMJ ... 1945) To demonstrate the organism in ulcers Cameron and Muir (Lancet 770 194..) removed the membrane applied saline compresses for 4 hours, then scraped *the surface at the margin to obtain material for cultures* They described acute primary infections as small follicular blisters or pustules becoming flat sores while as a secondary invader *C diphtheriae* caused the rapid development of a blackish membrane *Of their* 66 cases with cutaneous lesions, 4 were limited to the skin and 1 developed paralyses. Deep punched-out ulcers seen in the South Pacific region were diphtheritic in many instances reported Liebow et al. (AIntM 8: 255, 1946) Trauma or an insect bite predisposed to the infection, and the granulations at the bottoms of the ulcers constantly underwent necrosis *Slightly alkaline blood agar* was good in bacteriologic identification, and penicillin in saline locally helped healing. The Schick test was twice as frequently positive in patients with such ulcers as in controls. The ulcerative diphtherial lesions seen by Stern (CalifM 69 ..4 1948) were generally painless and the scars they produced were hypoesthetic.



Fig. 371.—Pustular diphtheritic lesion of sole, 3 days' duration.
Fig. 372.—Diphtheritic paronychia, 14 days' duration.



Fig. 373.—Diphtheritic ulcer 10 days' duration, with rolled edges.
Fig. 374.—Desert sore with secondary diphtheritic infection, 6 weeks' duration.
Fig. 375.—Proliferative type of diphtheritic ulcer 7 days' duration.



Fig. 376.—Diphtheritic ulcer of 10 days' duration. Compare Fig. 377.
Fig. 377.—Same ulcer as Fig. 376, seen 8 days later.
Fig. 378.—Scar of diphtheritic ulcer which has been healed for a year.
(Figs. 371-378 courtesy of Dr. R. Gill. ADR 48: 408, 1944.)

Recalcitrant ulcers of the leg due to diphtheroid organisms were the result of rapidly progressive necrosis following initial necrotic pustules in the cases of Barber et al. (BJD 49 260 1937)

Toxic Erythema appearing as a rash on the trunk and extremities is a transient occurrence in some cases and annular erythematous lesions may be seen (Robinson: JCutDis 1: 193, 1933)

The Guillain Barré Syndrome of upper respiratory infection followed by diplopia paresthesias, disability of the lower extremities, high protein content but no other abnormality of the spinal fluid, and myocardial damage, is perhaps diphtheritic and skin diphtheria may produce it according to Delp (AnnIntM 24 618 1946) Myocardial involvement was better detected by electrocardiogram than by clinical examination the more striking abnormalities occurring in the T waves; palpitation was not a symptom, but dyspnea and dizziness when erect, and abdominal pain, nausea and breathlessness were noted by Kay and Livingood (BullUSAMD 4: 462, 1946) Heart damage following cutaneous diphtheria was reviewed in an editorial (BMJ 1: 338 1947)

Multiple Neuritis caused by cutaneous diphtheria was of especial interest to Gaskill and Korb (ANeurPsych 55 559 1946) The onset was late, averaging some 70 days after the initial skin infection. It occurred in only 14% of patients who received antitoxin during the first month, but appeared in 30% of those given antitoxin later than this. Cranial nerve palsies and peripheral paresthesias were observed, and, once they had developed, were unresponsive to treatment. Twenty cases of late polyneuritis were reported by Sampson (AmJMSc 1 433 1946)

The Schick Test is a means of distinguishing between the susceptible and resistant members of the human herd. It is performed by the intracutaneous injection of toxin, to which a positive reaction, an erythematous wheal, means antitoxin is absent or inadequate. The Schick test may not be relied upon as a definitive measure of immunity and repeated doses of toxoid should be given in prophylaxis (Sandesson et al. J 112: 1919 1939) The test is followed in rare instances by an immediate allergic reaction (Beck: DelaSMJ 13 96 1941) The site may show reactivation if toxoid is given 9 days later (Chesney: BMJ 1: 911, 1936) Peripheral to a strongly positive Schick test reaction an area of anesthesia may be found 10 days later and this slowly diminishes during the subsequent 3 months (Toleman BMJ 1 1061 1935)

A scratch test using diphtheria toxin, 30 flocculating units per cc., seemed as reliable as, and easier to perform than, the intradermal test, wrote Groxin (AmJDisChild 57: 564 1939)

Diagnosis depends on suspicion, suggestive clinical features, and in the end cultural identification of the organism and tests of its virulence. A test of dubious value consists in applying 2% potassium tellurite to the lesion blackening which develops in 5 to 10 minutes indicates the presence of diphtheria or diphtheroids (Manzullo BMJ 1 1291 1939) Virulence of the organism may be tested by inoculation of the chick chorioallantois (Evans Sci 113 39 1951) Toxigenic strains kill the embryo in 96 hrs. in almost all cases, while nontoxigenic strains permit survival

Treatment requires isolation, penicillin locally and by injection and antitoxin, 20 000 units intramuscularly with careful precautions against anaphylaxis (BullUSAMD March, 1945) Antitoxin does not hasten healing While C diphtheriae is penicillin sensitive and the antibiotic should be given, antitoxin is equally necessary (Dodds BMJ 2 8 1946) Penicillin is effective in treating both the acute infection and the carrier state of which it terminated 87% of the 52 cases of Crawford (NEngJM 238 220 1948) Aureomycin is of considerable but not invariable value (Karelitz et al JPediat 39 544 1951) Terramycin seemed satisfactory both in diphtheria patients and in carriers reported Lall and Karelitz (JPediat 43 35 1953) Danger is great to both the patient and his associates because of the likelihood of delay in diagnosis. Antitoxin given early and in adequate amounts is curative Powdered methylene blue is a suitable topical application.

See Livingood et al (JID 7 341 1946) reviewing 140 U S Army cases Liebow et al. (AIntM 78 255, 1946), neurologic complications and laboratory diagnosis Denhoff and Kolodny (ADS 55 344 1947) relation to tropical ulcers Church and Mason (ADS 56 35 1947) diverse lesions of extremities, abdomen, genitalia Damon (NYSJM 24 1029, 1924) Vossius (DWchn 101 462, 1935) penile gangrene, Borovsky (J 104 1399 1935) 13 penile cases Went (BMJ 2 1032, 1936) primary postal of finger McKee (CanMAJ 35 426, 1936) conjunctival, Jwarowskaja (DWchn 103 312, 1936), primary vulva in girls MacCarthy (BMJ 2 421, 1937) cases, postauricular and axillary intertrigo Melchior (PresseMed 45 1068 1937) in granulating wounds Santori and Labrance (GitalD) 79 75 1938) 7 cases in children resembling streptococcic dermatitis Petros (he ADS 41 131, 1938) [illegible] penile Morrison (KebrMJ 1940), 12 [illegible] cases Ra[illegible] (MunchMW [illegible] 87 62 1940) penile Morrison (KebrMJ 1940), 12 [illegible] cases [illegible] (ActDV 23 281 1944), external transmission [illegible] 29 61 1944) conjunctival Vogelsang and Nelson (ActDV 25 281 1944), external transmission of genital diphtheria Bottomley and Christie (JObGyn 54 378 1947) cervix and

urethra, fatal case; Schwartz (Dermatologica 93 87, 1946) 27 cases Reiss (ADS 56: 216, 1947), cases resembling lymphopathia venerea and Stevens-Johnson syndrome, Hixby (ADS 58: 381, 1948) primary postular LaCoulant and Bourrell (Annd D 78 300 1951) impetigi noid and varicelliform cases.

PSEUDOMONAS AERUGINOSA INFECTION

Symptoms.—*Pseudomonas aeruginosa (B pyocyaneus)* has occasionally caused an ecthymatous or gangrenous dermatosis. A patient with septicemic symptoms and abscesses which became gangrenous lesions simulating glanders was described by Carter (Lancet 1 437 1924) Infants and children rarely adults, are affected and undernutrition or cachectic states are predisposing factors. The lesions are livid, indolent abscesses measuring up to an inch in diameter They are multiple develop rapidly and are capped by a vesicle or bleb which ruptures to form a superficial ulcer with a necrotic center *Ps. aeruginosa* may cause middle-ear suppuration ecthyma gangrenosum, necrotic and ulcerative lesions of the alimentary mucosa perhaps infantile diarrhea. It is usually however merely saprophytic and occurs in feces and on the skin about the axillae and anus, commonly contaminating eczematous dermatoses and ulcers. It cannot grow in an acidic medium. No reason is known to explain its occasional pathogenicity but ear canal infections with this organism are common and difficult to cure The dermatitis produced is exudative and itchy but clinically nondescript

Septicemia cases especially were studied by Hand (SouthMJ 47 1049 1954) who secured 3 recoveries in 5 cases by the use of polymyxin B Skin lesions in such cases are important because they may be recognized sufficiently early for therapy to be of value. They begin as minute ecchymoses or blebs at a time when the blood culture is usually already positive, although the infant s temperature may still be normal (Geppert et al. JPediat 41 555 1952) The blebs persist or enlarge and undergo crusting or produce weeping lesions. Large areas become dry dark and necrotic suggestive of thrombotic necrosis. The extremities and buttocks are the sites of predilection. Many cases have been reported as ecthyma gangrenosum (McCurdy and Noter Pediat 9 572, 1952) but the lesions were recognized as characteristic manifestations of *Ps aeruginosa* sepsis almost 40 years ago by Fraenkel (ZtschrHyg 84 369 1917) Good clinical photographs were presented by Geppert et al. (1952) who noted the peculiarity of the histologic findings in that vascular thromboses are common while the inflammatory tissue reaction is minimal perhaps as a result of the potent proteolytic enzymes produced by the organism (Yow and Townsend AmJMed 14 762 1953)

Diagnosis.—The presence of the organisms is proved by culture, although a putrid odor of the exudate is strongly suspicious. When *Ps. aeruginosa* infects the ear there are usually other pathogenic bacteria also present see Dermatitis of the External Ear Infections with this organism are becoming more frequent, it would seem, because of the suppression of other organisms with the commonly used antibiotics (Clement and Milland: PresseMéd 61 661 1953)

Treatment.—Supportive measures are recommended, keeping the skin dry with alcohol and powders, and the ulcers dry also with boric acid or other mild antiseptic preferably in powder form while ultraviolet light and foreign protein therapy may be helpful. Weak solutions of acetic or citric acid or 0.5% phosphoric acid are beneficial for local application (Weidman Appleton s System of Medicine 1937) Streptomycin sensitivity of *Ps. aeruginosa* was demonstrated by Bellows and Farmer (J 135 491 1947) in experimental eye infections where instillations of a solution of 10 000 micrograms per cc. were safe and effective In dermatitis of the ears compresses and instillations of 2,500 units per cc cured a case of Calloway (ADS 55 257 1947) Recalcitrant exudative dermatitis of the foot followed trauma and was unresponsive to many therapeutic agents until zinc peroxide was used by Post and Hopper (ADS 63 220 1951) Proteus may thrive during therapy with an antibiotic

which depresses other organisms, according to Yow (J 140 1184 1952) who recommended polymyxin B Chloromycetin 0 6% in Vioform Cream, is an effective topical application.

See Hitschmann and Kreibich (WienKlinWchn 10: 1093 1897) ecthyma gangrenosum; Dudden (JahrbKinderh 99: 257 1922) 4 fatal gangrenous cases, Carter (Lancet 1: 447 1924) septicemia and baccemia, resembling glanders Yap (ArDuS 178 687 1939) multiple ulcers cured with $KMnO_4$, H_2O_2 and zinc peroxide.

NECROBACILLOSIS

An acute infectious disease has been described in the human being caused by B necrophorus a non-spore-bearing elongated gram variable filamentous anaerobe to which are attributed calf-diphtheria, necrotic stomatitis of cattle, foot rot of sheep gangrenous dermatitis of horses and mules, and hepatic necrosis of cattle, pigs and sheep (Beveridge: JPathBact 39 467 1934) *Bullae and erysipelas-like disease developed following a scratch* of a meat inspector s hand, but recovery ensued after a stormy week, in the case of Stemen and Shaw (JKansaMS 10: 405, 1910) No lymphangiitis or constitutional symptoms occurred in the case of Bamber (BJD 53: 351, 1941) Subcutaneous abscesses of 8 years duration with gas formation characterized the case *of Reuter (Trans. ADA 1948, unpublished)*



Fig. 379 —Necrobacillosis of the hand. (Dr F W Shaw)

TUBERCULOSIS OF THE SKIN

Cutaneous infection with *Mycobacterium tuberculosis* may be primary or secondary the skin being involved by inoculation directly or from an internal focus. Manifestations of tuberculosis in the skin depend on the presence and activity of *Myco tuberculosis* or its products, and on the reactivity of the tissues of the host. This reactivity is a significant variable involving the newness of the infection or its superimposition on a background of previous infection which has altered immunity and sensitivity Immunity and sensitization are perhaps independent phenomena although the independence may be only partial as is shown by the fact that hyposensitization by injections of tuberculin does not necessarily alter immunity (Selter and Weiland ZtschrfTuberk 74 161 1935) Clinical appearances vary according to the predominance and histologic location of the tubercles, the inflammatory process, *the granulation tissue or the secondary changes such as hypertrophy* or hyperplasia of the epidermis, or degeneration necrosis or ulceration of the affected parts (Sulzberger and Wise MCNAm 14 1555 1931)

CLASSIFICATION OF TUBERCULOUS LESIONS OF THE SKIN

Localized types of cutaneous tuberculosis extending from an infected spot, progressive in the absence of adequate immunity

1 Primary tuberculous complex in the skin (Ghon tubercle; inoculation into virgin soil)
2 Tuberculosis verrucosa cutis (inoculation into partly immune soil)
3. *Tuberculosis cutis orificialis (secondary by implantation from disease of internal organs)*
4 Scrofuloderma (secondary t subjacent glandular or osseous involvement)
5. Lupus vulgaris

Hematogenous types of cutaneous tuberculosis

1. Acute miliary tuberculosis (not limited to the skin occurs usually in children, is ge eralized and fatal; immunity lacking)

2. Multiple disseminated tuberculosis of the skin (immunity inadequate to prevent caseation)
   a. Disseminated miliary lupus of the face
   b. Rosacea like tuberculosis
   c. Tuberculosis cutis indurativa: erythema induratum; tuberculous gumma
3. Tuberculid with hyperergic immunity
   a. Lichen scrofulosorum
   b. Papulonecrotic tuberculid
4. Tuberculid with hypoergic immunity: sarcoid (questionably tuberculous)

See Gans (Histologie der Hautkrankheiten, Springer 1928, p. 416); Volk (Handb HuG 10: 1-686, 1931), McCarthy (Histopathology of Skin Diseases, Mosby 1931 p. 239); Schmidt (AfDuS 176 639 1937) Montgomery (ADS 35: 698 1937); Blumenthal (ADS 35: 1027, 1937), relation of type of lesion element to allergy and immunity Cipollaro (NYSJM 44: 1557 1944); Michelson and Laymon (ADS 52 108, 1945); Riehl and Kopf (Hauttuberkulose und ihre Therapie, Vienna, 1950)

Localized Tuberculosis Extending From an Infected Site

The Primary Tuberculous Complex is characterized by the development of an ulcer at the site of inoculation accompanied by lymphangiitis and lymphadenitis. Bacilli are present in the tuberculous chancre as well as in its satellite gland which may or may not undergo caseation and ulceration. This syndrome occurs when tuberculosis is inoculated into virgin soil. The 3 cases I have seen occurred in physicians who were inoculated while performing autopsies, a hazardous task in tuberculous deaths. Two of them healed after extremely tedious courses while one died following dissemination of the disease after the axillary nodes became scrofulous. Records of 28 primary inoculations of the skin and mucous membranes were presented by Miller (Lancet 1 5 1953) who noted that erythema nodosum followed the infection and calcification of the regional nodes developed in every one

Cases of inoculation seemingly with *M tuberculosis* have followed minor injuries incurred in swimming pools, and have been described by Cleveland (ActaD-V 31: 147, 1951) and Tolmach and Frank (J 151: 7?4 1953) An acid fast organism, *M. balnei* was originally identified from biopsies as well as the water and walls of a pool where a number of patients remembered having scratched the inoculation site, reported Linell and Norden (ActaTuberc Scand Supp. 33, 1954 also BJD 67: 39 1955) These authors studied cases involving 61 girls and 19 boys who in 1949-1951 acquired the localized granulomatous lesions in one town in Sweden. The incubation period was about 3 weeks. A small, red papule came first, usually on the outer aspect of the elbow It increased gradually for weeks or so becoming soft, spongy and eventually crusted over a central crater Spontaneous healing, followed by scarring took place after several months. Adenopathy usually absent was inconspicuous when present. In many cases the lesions were trivial, but in a few, suppuration occurred and lasted as long as 3 years. Several patients were infected twice at intervals of 1 to 6 months. Linell and Norden inoculated human volunteers and succeeded in reproducing the disease. Their bacteriologic studies indicated that their *M balnei* is not a form of *M tuberculosis* In vivo it was sensitive to streptomycin, tyrothricin and isoniazide. The histologically tuberculoid lesions it produced were not responsive to Finsen light calciferol or PAS. In 1952 another epidemic in a different Swedish town provided 24 more cases, and these patients underwent contemporary Mantoux conversion seemingly due to the swimming pool infection and indicative of immunologic similarities between *M balnei* and *M tuberculosis*.

See Ghon (BeitrPathAnat 69 66 1921) primary complex; Stokes (AmJMSci 169 722, 1925) earliest U.S. report of skin inoculation Brunsgaard (BJD 46 112, 1934); Michelson (ADS 32 889 1935) tuberculous chancre; Montgomery (PSMMQ 11 407 1936), Sulzberger (J 106 314, 1936), Schachmann (AfKinderh 116 31, 1939) 4 cases in infants Laymon (Jour Lancet 59 124, 1939), 2 cases, O'Leary and Harrison (ADS 44 371 1941) good description Scott (AmJDisChild 62 596, 1941) petellar inoculation in child causing verrucose tuberculosis; Vero (ADS 44 736, 1941) lesion in physician contracted at autopsy, Pitcherska and Bedam (AOphth 30 198, 1944), conjunctival primary Epstein (ADS 91 317 1948) Grady (AmRevTuberc 63 576, 1951) comprehensive review Russell (BJD 65: 33, 1953) Miller (Lancet 1 5, 1953) cases, 16 of skin, 6 of eye, 3 of mouth Zschunke and Irmscher (Hautarzt 6: 118, 1955) occupational, in a milk tester case

Tuberculosis Verrucosa Cutis.—Infection occurs from without as a result of an ulcer at the site of inoculation accompanied by lymphangiitis and tuberculous sputum. Sites of predilection are the exposed parts of the body The lesions begin with small wartlike papules which gradually increase in number and coalesce to form small verrucose rounded reddish-brown patches. The lesions may heal spontaneously first centrally leaving thin atrophic, whitish cicatrices. Streptomycin injections cured cases of Allison et al. (JID 13 ?07 1949) and Kern (ADS 63 378 1951)





Fig. 380.—Tuberculosis verrucosa cutis, antecubital location, 9 years' duration, in a 13-year-old boy. (Dr. Glover Wende.)

Fig. 381.—Tuberculosis verrucosa cutis of buttock. (Dr. Robert M. Andrade.)





Figs. 382 and 383.—Tuberculosis verrucosa cutis. (Dr. J. R. Shelmire.)





Fig. 384.—Tuberculosis verrucosa cutis. (Dr. William A. Pusey.)

Fig. 385.—Tuberculosis verrucosa cutis.

Verruca Necrogenica or prosector s wart is a form of tuberculosis due to inoculation. Lesions are seen most frequently on the dorsal surface of the thumb and fingers. They are usually indurated, and always keratotic The growths are persistent but benign, and disappear spontaneously with but slight scarring if immunity is high

Tuberculosis Cutis Orificialis attacks the integument contiguous with mucosal orifices. It begins with the formation of yellowish miliary tubercles, which usually ulcerate to form sluggish, granulating painful sores. The progress of the disorder is slow The lesion is usually superficial with soft irregularly outlined edges, and a raw uneven floor covered with purulent fluid When the tongue is attacked the patient suffers great pain and discommodation (Schugt Laryng 51 284 1941)

See Morrow and Miller (J 83 1482, 1924) 10 tongue cases Rautschkolb (ADS 29: 308, 1924) Stahler (AmJSurg 43: 419 1938), 11 rare lip cases Bryant (AmRevTuberc 39 38, 1939) 17 oral cases in 7 000 patients with advanced tuberculosis, good description, tooth socket is not infected after extractions Farber et al. (AmRevTuberc 42 766, 1940) tongue cases rare may occur as extension from larynx Ikes and Redding (J 117 1148 1941) anal case Lewis (JUrol 50 737, 1940) penile involvement of 110 cases, 73 resulted from circumcision, usually primary; Wolfer et al. (J 136 249 1948) improvement on streptomycin; Butaille and others (abs JID 62: 237 1950) oral cases including oral primary; Wallner et al. (J 146 1252, 1951) 10 laryngeal cases treated with streptomycin, some with PAS, too, with marked improvement and usually relief from pain, Kidd et al. (AmJSurg 82 884, 1951) anorectal streptomycin an adjunct to surgical treatment.





Fig. 336.—Tuberculous ulcer of tongue (Dr George M. MacKee.)
Fig. 337.—Tuberculosis of the tongue. (Farber et al: AmRevTuberc 42 766, 1940.)

Lupus Vulgaris is characterized by plaques of small, soft, apple-butter like tubercles. The malady progresses by the formation of satellite nodules, which coalesce to form irregular groups of various sizes. The face is the common site although no part of the body is exempt. The course is slow but progressive Regressions with subsequent atrophy may take place, but as a rule the tubercles become small, crusted ulcers, ultimately to be replaced by fibrous tissue Deformity resulting from ulceration, cicatrization and contraction may be great The disease develops slowly and insidiously and the chronic course is characterized by periods of retrogression and exacerbation for many years (Michelson JID 7 261 1946) The extent of the disease may become extreme and serpiginous and ulcerative cases sometimes with elephantiasis, have been described (Volavsek AfDuS 178 288 1938 Hamann: abs J 114 1603 1940) Traub (ADS 42 1152 1940) presented such a patient, who obtained a remarkable cure with plastic surgery Lupus vulgaris has in rare instances developed at the site of BCG vaccination (Marcussen: BJD 66 121 1954) Even if BCG vaccine does occasionally incite lupus vulgaris, this is rare and the harm it does is outweighed by the good (Edit BMJ 2 1095 1954); see Letter from Norway (J 155 61 1954)

Scrofuloderma comprises cases in which the skin is involved secondarily by direct extension from subcutaneous lymph nodes or bones which are tuberculous. Cervical lymph nodes are those most commonly affected. Infected nodes become swollen, firm and adherent to the overlying skin They





Fig. 388.—Lupus vulgaris. (Dr Grover Wende.)
Fig. 389.—Lupus vulgaris. (Dr D. E. H. Cleveland.)





Figs. 390 and 391.—Lupus vulgaris. (Dr Gustav Riehl.)

are at first nodular and elastic but later as a result of caseation may become doughy and ultimately fluctuant. Overlying skin becomes thinned, purplish and depressed and sloughs at one or more points. The resultant ulcers serve as mouths of sinuses from which purulent matter discharges. The sinus walls are soft, reddish and granular and bleed readily. Symptoms and constitutional manifestations are slight. The lesions may heal spontaneously with the formation of rough, corded cicatrices, or the disease may persist for years with little change. Most patients are children and young adults.



Fig. 332.—Lupus vulgaris, papillomatous and elephantiasic. (Dr Gusta Riehl.)





Figs. 333 and 334.—Lupus tumidus. (Dr Gusta Riehl.)

Pathology.—*Mycobacterium tuberculosis* gives rise to histologic changes in the dermis which do not differ from those resulting from its presence in other tissues of the body. The essential lesion is the tubercle or tuberculous nodule. The epidermis is not involved primarily but is usually stretched and



Fig. 395—Extensiv lupus vulgaris with egetativ squamous carcinoma in region showing atrophy from x ray therapy



Figs 396 and 397—Carci oma in l pu lgaris (Dr Gusta Riehl)



Fig 398.—Scrofuloderma. (Dr Gusta Riehl)



Fig. 399 —Scrofuloderma. (Dr Robert Andrade.)





Fig 400.—Scrofuloderma. (Dr Robert Andrad)
Fig 401 —Scrofuloderma cicatrisatum. (Dr Gusta Riehl)

thinned as a result of pressure from below Bacilli are numerous in lesions associated with low immunity and scarce in those with hyperergy They may be undemonstrable in hypoergic individuals whose immunity is high.

Chemical fractions of dead tubercle bacteria were used in investigations by Sabin and Joyner (JExperM 68: 659 837 1938) who showed that specific fractions evoke typical responses. The phosphatid substance injected subcutaneously provokes an epithelioid and giant-cell reaction; the waxes, proliferation of fibroblasts the acetone-soluble lipid, proliferation of all connective tissue cells including those of the vessels, even causing hemorrhage; the polysaccharides are chemotactic and toxic to leukocytes; the protein produces plasma cell proliferation and fever

Tissue responses depend also on factors of sensitization and immunity that are incompletely understood (see Rich: Pathogenesis of Tuberculosis, Thomas, 1944 Friedman: AmJ Path 23: 621 1944 asteroid bodies in giant cells of sarcoid) Explants from an immune donor retain acquired immunity which appears to be concerned with fixed tissue cells, mononuclears and phagocytes but no circulating antibody is demonstrable (Edit.: J 119: 1508, 194.) Acquired tuberculin hypersensitivity is not transmitted by serum from a hypersensitive guinea pig (Chase: PSExpBiol 59: 134 1945) but leukocytes obtained from peritoneal exudate of the donor do convey hypersensitivity when injected intradermally into the recipient animal (Kirchheimer and Weiser: PSExpBiol 66: 166, 1947) This kind of phenomenon was demonstrated in human beings by Lawrence (PSExpBiol 71: 516, 1949) who found that hypersensitivity so acquired persisted for as long as three months. See Edit. (J 138: 833 1948 141: 1301 1949)





Fig 402—Tuberculous tissue from a miliary sarcoidal lesion, showing giant cells and epithelioid cells, but no caseation

Fig. 401.—Lichen scrofulosorum, showing tuberculous inflammation superficially located in the dermis. (Dr Stuart Way)

A carbohydrate-lipid component of dead bacteria, obtained by paraffin oil extraction, was claimed to provoke antibody formation just as Old Tuberculin does, by Choucroun (Sci 106 46 1947)

Clinical tuberculosis must be recognized a a struggle between the tubercle bacillus and the tissues of an immunized host, wrote Pottenger (AmRevTuberc 68: 933 1953) in his essay correlating immune mechanisms, pathologic changes, symptoms and treatment. It may be described as a metastasizing inflammatory, destructive and curative process. The patient kills himself or cures himself according to the metastases which take place the number and virulence of the bacilli which cause them, and the state of his resistance natural and immunologic, at the time the metastases form or that he is able to develop in response t their stimulation. While the immunity reaction is the cause of destruction of tissues, at the same time it is the most important aid in the cure of the disease and one without which there would be no recovery

See Jadassohn (BJD 41 481, 1922) tuberculoid structure develops when immunity is high so that organisms are few Dienes and Mallory (AmJPath 13 897 1937) responses to injection of tubercl bact ria differ as early a the 4th day in infected as compared with previously noninfected animals Kahn (AmRevTuberc 20 150, 1929) dust-fine particles of H37 strain of tubercle bacteria sprout rods which grow int mature organisms Sabin et al (JExpM 52 suppl. 3 1930) results of injecting chemical fractions of M t berculosis Smithburn and Sabin (JExpM 56 867 1932) tissue reactions to chemical fractions; Anderson (PhysiolRev 12 166, 1932) chemical fractions Wells and Long (The Chemistry of Tuberculosis, Baillière, Tindall & Cox, 1932)

Prognosis of Tuberculosis Cutis.—Lupus vulgaris is extremely chronic rebellious to treatment and prone to relapse and recur Systemic tuberculosis is present or develops in a considerable proportion of the cases. The outlook in miliary and disseminated tuberculosis is even graver Tuberculids are benign in themselves, but they may signify an awakening of the systemic disease

The mortality rate for pulmonary tuberculosis in some 3,500 cases of lupus vulgaris was from 5 to 10 times as high as among the normal population the rate was significantly higher for males than for females (Kalkoff AfDuS 186 144, 1947) Modern treatment is highly effective

LUPUS CARCINOMA is a recognized hazard squamous carcinoma developing in the scars, especially when x ray therapy has been used. The lesion may histologically resemble spindle cell sarcoma, yet is of epithelial derivation. Cancer developed in 3% of 2 725 cases of lupus and caused 1.2% of the deaths, reported Mayr (DWchn 104 51 1937) See Spindle Cell Carcinoma also Schock (DWchn 97 1723 1933) Guell (abs J 148 152, 1952) If early lesions are recognized and treated effectually the precancerous proclivity of the tuberculous scar can be counteracted with success.

Diagnosis of Tuberculosis Cutis.—So various are the clinical configurations under which tuberculosis may appear that as in syphilis, suspicion of its possible existence and broad knowledge of its manifestations are required for diagnosis. Biopsy and animal inoculations are two reliable means for diminishing equivocation. Tuberculous lesions are to be differentiated from those of carcinoma, syphilis, lupus erythematosus and blastomycosis. In lupus vulgaris the nodules develop in previously sound skin and are always soft and compressible. Under a pressure glass outlying tubercles appear as yellowish apple-butter-colored puncta surrounded by exsanguinated sound skin. Tuberculous ulcers have soft, nonelevated margins, and their bases are usually granulating and pliable

TUBERCULIN TESTS.—Negative test may signify positive or negative anergy Quantitative intradermal testing has significance (Bonnevie and Björnstad ActaD-V 21 9 1940) Tuberculin patch tests are simple harmless and fairly reliable (*Vollmer and Goldberger AmJDisChild 57 1272, 1939*)

That tuberculous lesions can *always* be found in bodies of persons who during life had no evidence of disease except reactivity to tuberculin was demonstrated by Ghon the tuberculin test demonstrates the presence of tubercle bacilli in the body of the patient as surely as though they were seen through a microscope or were grown in culture media or in animals, according to Myers et al. (J 158 1 1955) Sensitization develops within 3 to 7 weeks after invasion, so that tests frequently repeated will determine the date of invasion promptly and accurately

Reaction to a tuberculin test, patch or intradermal, signifies that at least primary lesions are present, and they probably contain living tubercle bacilli (J 139 69 1949) After the bacilli first invade the body there is an interval of from 3 to 12 weeks before the tissues are so sensitized that reactivity can be elicited by tuberculin (Sweany: AmRevTuberc 56 125, 1947) When allergy first appears, it soon reaches a high level, but if no exogenous or endogenous reinfection occurs, sensitivity wanes until it can be elicited only by a large dose of tuberculin, such as 1 mg Reactivity may sink even below this level, and, if all tubercle bacilli die in the body which probably happens more frequently than used t be believed, allergy completely disappears so that there is o response even to 10 mg. of tuberculin.

Every reactor, child or adult, should be examined at once to determine whether lesions can be detected. If none is found, he should be re-examined periodically The adult who reacts to tuberculin should have the test repeated periodically to determine whether sensitivity wanes or disappears. Tuberculous disease may become evident at any time as long as allergy persists. The old belief, once a reactor al ays a reactor, must be abandoned, although it is not known how long allergy lingers after all tubercle bacilli have died. The belief that all adults have had primary tuberculous infection and therefore react to tuberculin is now obsolete in most parts f the United States. It is as important to test adults as to test children, and the significance of the results is the same.

Atypical tuberculin reactions attracted the attention of Arany (J 15_1 491 1953) In 6 instances, there appeared a large area of marked erythema and a small area of infiltra

tion at 24 hours, completely waning at 48 hours usually following a large dose of intracutaneously administered tuberculin. These are false positive reactions as a rule, Arany thought, but may rarely occur during certain phases of active tuberculosis. Therefore if this type of reaction is encountered in a patient with pulmonary lesions of undetermined nature, it should not be interpreted as definite evidence against the diagnosis of active pulmonary tuberculosis.

The histology of the intradermal tuberculin reaction in human beings was investigated by Hinshaw and Feldman (JID 43 1939). They did not find such obliterative endarteritis as is seen in these lesions in cattle.

See Sulzberger and Wise (MClinNAm 14 1555, 1931) quantitative reactions, relation of reactivity to clinical forms, positive and negative anergy; Martenstein (AfDuS 158: 409, 1929) clinical forms and tuberculin reactivity. Sulzberger (AmRevTuberc 28 734 1933), in sarcoid. Sutherland (The Tuberculin Handbook, Oxford Univ Press, 1936). Moro and Doganoff (WienklinWchr 20 933, 1907) O T in wool fat for patch testing. Wolff and Hurwitz (J 109: 2042, 1937) patch tests. Hays et al. (AmJMedSci 194 220 1937) monthly tests in tuberculous patients showing no correlation of sensitivity and clinical course, though dying patient was insensitive. Harrington et al. (J 108 1309, 1937), incidence of positive reaction by age groups, worthless in treatment. Puente (abs YBD 1937 p. 79) patch test. Nelson et al. (JPediat 12, 26, 1938) tuberculin test does not sensitize. Corper and Cohn (J 112 403, 1939) specific immunity not producible with vaccinal preparations. Thomas (ADS 45 544, 1942), purified protein derivative (PPD) as good as O T; Pascher and Sulzberger (ADS 49 258, 1944) agreement between O T and Vollmer patch test. Lowenthal (ADS 52 240, 1945) Vollmer negatives should be retested with 0.01 O T. Kalkoff and Huck (AfDuS 186 374, 1947), threshold sensitivity in various forms of disease. Leider and Sulzberger (JID 13: 249, 1949) O T reactions in city dwellers by age groups, BCG vaccination effects. Stilwell (PSMMC 25 436, 1950) tuberculin testing and evaluation.

Treatment of Tuberculosis Cutis.—Hygienic measures are important in this form of the disease as in systemic infections. Fresh air sunlight, ample nourishing food and moderate exercise are helpful.

Vitamin D_2 was reported to yield remarkable improvement in lupus vulgaris and was usually tolerated in a dose of from 200 000 to 400 000 units per day (Dowling and Thomas BJD 58 45 1946). Its use entails hazard of metastatic calcification of kidneys and vessel walls, as well as less consequential symptoms of intoxication.

Macrea (BJD 59: 38 1947) obtained excellent improvement in most of the 70 cases of lupus vulgaris so treated. Michelson and Steves (ADS 56 317 1947) helped 6 cases, obtaining scarring fibrotic healing with a dose of 150 000 units of viosterol in oil per day.

The use of vitamin D_2 was initially tried in 1940 by Charpy (BJD 60 121 1948) and independently by Dowling and Thomas (see BJD 60 1?7 1948; BMJ 1 430 1948 Lancet 1: 919 1946). Its action appears to be concerned with mineralization of the skin, with biochemical changes comparable with those promoted by the salt free diet. Its helpfulness is not reliable, and it does not replace Finsen light treatment, wrote Ingram and Anning (BJD 60: 159 1948).

Toxic reactions from overdosage of vitamin D (q.v. under Avitaminosis) include nausea, anorexia, vomiting cramps, diarrhea, urinary frequency tenderness of gums and teeth, arthralgia and myalgia, dizziness, weakness headache haziness of memory and paresthesias of the extremities (Bills: PhysiolRev 15 1 1935). Some 111 cases of hypervitaminosis were reviewed by Chaplin et al. (AmJMedSci 21: 369 1951) who listed, in addition to the above depression mild psychosis and stupor normocytic, normochromic anemia albuminuria, red blood cells and casts in the urine, with progressive impairment in concentrating ability frequency and nocturia band keratitis elevated serum calcium and phosphorus with normal or slightly elevated alkaline phosphatase progressive nitrogen retention diffuse demineralization of the bones in advanced cases, and periarticular soft tissue calcification. Depending on the severity of intoxication all or only a few of these findings may be present. Six of their patients exhibited band keratitis, a lesion commonly associated with disturbed calcium metabolism. The 2 most serious of their 7 cases showed remarkable calcium-containing cysts, located largely in the periarticular areas and in the vicinity of the bursae. These cysts were fluctuant, did not transilluminate and ranged from 1.5 to 8 cm. in diameter. The calcium phosphorus ratio of the sediments centrifuged from the aspirated fluid of the cysts was more than twice that present in bone. Treatment of the patients consisted of cessation of vitamin D intake a strict low-calcium diet, avoidance of undue exposure to sunlight, avoidance of alkali, maximum mobilization of the patient and sufficient fluid intake for a daily urinary output of at least 2,000 cc. Some of the patients were given diethylstilbestrol.

Vitamin D is a potentially dangerous drug and should be used only in diseases in which there is a reasonable rationale for usage. If it is used in massive doses, careful follow up is obligatory for early detection of signs of intoxication. A rise in serum calcium follows D_2 treatment and is a good indication of incipient toxicity (Dawson BJD 60: 164 1948). Constipation is an early toxic symptom (Gauvain BJD 60: 1?4 1948). D_2 may cause conjunctivitis and ulcerative necrosis of lupus tissues, and it is not well tolerated by hyper

tensive patients (Lomholt: BJD 60: 13., 1948) Cysteine 1 mg. by injection daily, inhibiting the action of alkaline phosphatase seemed an effective antidote in intoxication from D_2 (Charpy and Pichat: also Lancet 1: 433, 1948)

Inactivated ergosterol is nontoxic and is as beneficial in a dose of 300 to 600 mg per day intramuscularly as vitamin D_2, wrote Raab (Sci 106: 546, 1947)

Yet the remarkable improvements on D_2 treatment are most marked during the toxic phase of the administration of the drug (Edit. BMJ 1: 453, 1948) During healing, the tuberculous tissue diminishes and is replaced by young connective tissue (Freudenthal: BJD 60: 178, 1948) Comparing clinical results with histologic changes, tuberculosis histologically active in lesions seemingly cured was found by Ruiter and Groen (BJD 62: 15, 1950) who warned against overrating the results. Histologic changes during treatment, with evolution to sarcoidal structure followed by scar were observed by Kovacs (also YBD 1949 p. 471)

See Anderson (EdinMJ 54: 552, 1947) 71 cases; Feeny et al. (Lancet 1: 433, 1947) 150 cases. Riehl (WienKlinWschr 60 525, 1948) 150 cases, Edit. (J 141 726, 1949) Anning et al. (QuartJM 17 203 1948) D_2 intoxication Pascher et al. (JID 13, 89, 1949) utility of D_2; Jeans (J 143 177 1950) hypervitaminosis Hyd and Richmond (AmJDisChild 80: 379 1950) chronic intoxication.

Streptomycin will usually induce fairly prompt apparent cures of skin lesions but histologic tuberculous changes persist and disconcerting disseminations of tuberculous disease such as meningitis and peritonitis, have followed its administration.

If streptomycin is given, the minimum dose should be 2 Gm. per day said O'Leary et al. (ADS 55 222, 1947) and most benefit accrues in scrofuloderma. See Council Rpts (J 135: 634 1947; 138: 584, 1948 14.: 650 1950; 147: 253 1951: Veterans Administration hospitals experience) one Gm. per day suffices.

Toxic manifestations, especially labyrinthitis, necessitated stopping the antibiotic in 6% of the series. One gram a day or even only twice a week reduces toxicity without impairing therapeutic efficiency While the organism develops resistance to streptomycin in about 30% of the cases, the concomitant administration of para-aminosalicylic acid delays or prevents this (Bailey: AmJClinPath 21: 241 1951) Best responses occur in fresh lesions rich in bacilli, and the antibiotic is without virtue in tuberculids (Adorni: ADS 68: 378, 1953) Tuberculous sinus tracts reacted favorably and promptly to streptomycin injections, reported Brock (AmRevTuberc 58: 33 1948) Oral lesions respond well (Oppenheim et al.: AOtol 5 : 910 1950) Combining calciferol and streptomycin in the treatment of 5 patients with lupus vulgaris, Cornbleet (J 138: 1150 1948) thought the two drugs worked in synergism. Local intracutaneous injection of streptomycin was tried by Foster (ADS 63: 597 1951) with apparent success.

Para-aminosalicylic acid 8 Gm per day yielded gratifying results in 7 cases of Linros (ActaD V 31 217 1951)

The hydrazides of isonicotinic acid, iproniazide and isoniazide exert an important therapeutic effect in tuberculosis in a daily dose of 4 mg per kg body weight (Selikoff et al. J 150 973 1952) All cases of cutaneous tuberculosis treated with isoniazide in doses of from 3 to 8 mg/kg daily were benefited reported Latapi et al. (ADS 69 678 1954) Given alone or in combination with dihydrostreptomycin, isoniazide produced good effects in true tuberculosis of the skin in the experience of Holsinger and Dalton (J 154 475 1954)

Lingual and laryngeal lesions he responded well. Various forms of cutaneous lesions so treated by Grutz (MedWchr 94: 1297 195.) were helped. Lupus vulgaris unresponsive to calciferol and other measures did well on isoniazide (Goldberg and Simon: J 131 640 1953) The drug cured in 15 weeks a case of 40 years duration according to Obermayer et al. (JID 19 311, 1952) Good results in lupus vulgaris have been reported by Russell et al. (Lancet 1 964, 1953) Leider and Sawicky (JID 21: 49, 1953) reported notable benefit in 12 cases of lupus vulgaris, 7 of indurative tuberculosis of the skin, and 1 of ulcerative disease; and they saw some benefit from its use in 2 cases of leprosy It did no good in lupus erythematosus sarcoid or tuberculid. Striking improvements were obtained in several patients within 1 month, while toxicity was relatively minor, being manifested by vertigo and tremor in 1 patient, who could not tolerate 50 mg per day reported Dowling et al. (BJD 65 314 1953) The worst cases did well according to Brett and Braun-Falco (DWch 127: 1 1953) whose series included 4 cases of l pus, 1 of erythema nodosum and 2 of scrofula. Mucosal as well as skin tuberculosis was gratifyingly responsive observed Grutz (DWchr 1°7: 160 1953), who saw one instance of purpuric intolerance of the drug In most cases treated by Chakraborty et al. (BJD 65 310 1953) improvement was dramatic and was evident within a fortnight of therapy The response of tuberculids and tuberculoid leprosy was usually disappointing but l pus, scrofula and lepromatous leprosy responded well, reported Cornbleet et al. (ADS 68 536, 1953) although sarcoid was not helped. Large doses were not more effective than modest ones. All forms of tuberculosis of the skin re-

sponded favorably in the experience of Goldberg and Simon (ADS 68: 656 1953). Isoniazide in a daily dose of 4 to 6 mg./kg. body weight continued for 3 or 4 months after clinical cure did not fail to improve every patient of Paulus and Serin (Medizin. Jan. 22 1955) and no serious by-effect occurred. Peripheral neuritis accompanying isoniazide therapy is prevented by giving pyridoxine simultaneously for according to Biehl and Vilter (J 156: 1549 1954) isoniazide induces excessive excretion of vitamin B_6.

Some authorities have made use of a salt free diet (Haldin-Davis BMJ 2 539 1930). It was alleged to have produced results that surpassed those of any other method of therapy (Blumenthal and Funk Strahlenther 45 49 1932). Tuberculin capable of doing much harm was once discarded as being of no use. MacKee (JCutDis 29 307 1911) found it valuable in nonulcerating lupus and tuberculosis verrucosa cutis and least effective in the ulcerating forms. The dose was increased progressively but not to the extent of producing fever. Gold sodium thiosulfate or other salts may be given intravenously. Gold is beneficial in some cases, but intoxication must be carefully avoided (Neuber WienKlinWchn 53 1021 1940).

Roentgen therapy heliotherapy and phototherapy were among the physical agents used. Phototherapy by means of the Finsen lamp gave the best cosmetic results but was extremely tedious. It required great patience and a staff of trained specialists (Lomholt BMJ 2 291 1934; abs J 114 2345 1940. Edit BMJ 2 366 1943). Aitken (BMJ 1 160 1937) used carbon arc light baths with especially good effect in the glandular cases. Radiant heat was commended by Rusten et al. (AmRevTuberc 34 383, 1936). X ray therapy approved if expertly used by Koch and Birkenmaier (DWchn 96 210 1934) entails the hazard of inciting lupus carcinoma. Modest doses in the treatment of fresh, small foci were recommended by Uhlmann (ActaDV 21 529 1940).

Destructive agents of many kinds have a place in the treatment of lupus vulgaris. Acid nitrate of mercury applied to the nodule by means of a small swab produces necrosis, crusting superficial chemical ulceration and sloughing of the tubercle, which eventually heals with scar (Adamson BMJ 2 123 1920). Trichloroacetic acid, lactic acid, potassium permanganate crystals and electrocoagulation are among the agents that have been used (Cipollaro APhysTh 18 415 1937). Plastic surgery certainly has a place in the treatment especially of lupus vulgaris but the removal of a lesion may not prevent the appearance of new ones (Butterworth and Freed ADS 46 242, 1942. Robinson and Tasker ADS 57 293 1948).

Cortisone and corticotropin appear to have no place in the treatment of active tuberculosis as such, and in the presence of active tuberculosis the use of these drugs should be regarded as potentially dangerous (Edit J 149 1474 1952). Careful examination before during and after the use of these drugs is indicated even in the absence of known tuberculous infection, for there may occur exacerbation of an unsuspected lesion. See Treatment cortisone.

REFERENCES ON TREATMENT.—Burgess (BMJ 2 835, 1935) intradermal hydnocarpat. Wallace (BMJ 1 1141 1937), intradermal hydnocarpate. Tytler and Lapp (BMJ 2 748, 1942) Promin. Waksman (J 135 478, 1947), antituberculous antibiotics, streptomycin resistance. Karlson et al. (AmRevTuberc 62 345, 1950) neomycin more effective than streptomycin in guinea pig infections. Mertens and Bunn (AmRevTuberc 61 20 1950) thiosemicarbazones, 3 mg. per kg. p. effective in mucosal cases and recent lesions with good blood supply, not in miliary or meningeal. Edit. (J 145 342 1950) thiosemicarbazones, literature toxicity occasional conjunctivitis, rashes, nausea, depression of hematopoiesis. Hartz et al. (AmRevTuberc 63 4, 1951), viomycin, from a violaceous actinomycete Streptomyces floridae. Hurley (PresseMéd 59 1533 1951) modern treatment of 120 skin cases with Dh streptomycin, PAS; Council on Pharmacy and Chemistry (J 154 52, 1954) report on chemotherapy of tuberculosis. Marchionini and Rockl (Dermatologica 4 161 1953) rapid and consistent improvement with isonicotinic acid in 103 cases, mostly lupus. Marson (MinervaDermat 29 219 1954 abs J 156 745 1954) histologic changes due to isoniazide therapy in lupus vulgaris.

Hematogenous Types of Tuberculosis of the Skin

Acute Miliary Tuberculosis.—Eruptions may or may not be present. Purpura may occur. *The infection is overwhelming* and the tuberculin reactivity is likely to be anergic (Rubin AmRevTuberc 39 567 1937). Dusky erythematous crusted papules and subcutaneous gummatous nodules were seen in patients with skin lesions accompanying acute dissemination of tuberculosis reported Lees and Munro (BMJ 1 496 1934).

Multiple Disseminated Tuberculosis of the Skin.—The lesions are small, circumscribed collections of brownish scale-covered nodules which appear suddenly and are irregularly distributed over the face, trunk and extremities. They may undergo central caseation necrosis so as to form ulcers which heal slowly





Fig. 404.—Lupus miliaris disseminatus. (Dr Gusta Riehl)
Fig. 405.—Lupus miliaris disseminatus. (Wise and Satenstein ADS 4 [illegible], 1931)



Fig. 406.—Rosacea-like tuberculosis. (Division of Dermatology Dept. of Med Uni of Chicago, from Weiner Skin Manifestations of Internal Disorders, Mosby 1947)

Miliary Lupus of the Face is a disseminated form in which tubercles, scattered more or less *symmetrically on the face are manifest as small, yellow* ish discrete papules. They make their appearance sometimes coincidentally with an exacerbation of pulmonic tuberculosis. The eruption is chronic, un sightly but asymptomatic It favors the periorbital regions. Histologically the lesions show caseous tuberculosis. The *patients react to tuberculin* with moderate hyperergy Animals have been successfully inoculated with material from the lesions (Wise and Satenstein ADS 4 586 1921)

Disseminated follicular lupus (Fox) and acnitis (Barthélemy) are de scriptive *names more or less synonymous with miliary lupus,* and representa tive of the same phenomena see Ketron (BullJHH 26 111 1915) Malony (ADS 15 285 1927)



Figs 40 408 and 409—Hematogenous, noncaseating tuberculosis in a Negress

Rosacea-like Tuberculosis is characterized by minute discrete brownish or dusky red flattened papular lesions on the face They make their ap pearance suddenly and in crops and persist over a considerable period of time They differ from the lesions of rosacea in being not centrally located upon the face not usually pustular and not accompanied by seborrhea Intra venously administered gold sodium thiosulfate may yield prompt therapeutic effects in this disease Sensitivity to tuberculin is usually high, though Lay mon (ADS 54 232, 1946) found such variation of reactivity *in Minnesota* cases that he judged the test of little diagnostic importance

See Lewandowsky (Cor Bl f schw Ärzt 47 1280 1917), original description Wile and Gruner (ADS 31 174 1935) Machee and Sulzberger (ADS 31 159 1935) Rothstein (KyMJ 38 417 1940) Laymon and Michelson (ADS 42 625, 1940) Machacek (ADS 44 387 1940) Rothman (ADS 54 231 1946) Snapp (JID 13 175, 1949)



Fig. 410.—Lichenoid tuberculid, extensive eruption. (Ockuly and Montgomery: JID 14 415, 1950.)



Figs 411 and 412—Lichenoid tuberculid Hematogenous distribution of epithelioid tubercles d pic ted the histologic structure of sarcoid, although in some places caseation necrosis was observed. (Ockuly and Montgomery JID 14 415, 1950.)

Lichenoid Tuberculid.—Representative of the hematogenous forms of cutaneous tuber culosis this uncommon variety named by Ockuly and Montgomery (JID 14: 415, 1950) appears predominantly on the extremities, with symmetry of distribution, sometimes quite extensive, and not on mucous membranes. A case was reported by Crawford (ADS 40 950 1939) Ockuly and Montgomery referred to similar cases of Pick (AfDuS 69 411, 1904) and Civatte (AnndeD 37: 709 1906) Resemblance to parapsoriasis has been noted. A nonpruritic flat topped or slightly umbilicated papule f split pea size violet or brownish in color with overlying and adjacent telangiectasis, capped by a fine adherent scale, is typical. Similar lesion were among those present the prototypic instance f Boeck's sarcoid (q.v) Such lesions are discrete and grouped, often with an ular configuration. They involute to form brow ish macules without scarring Histologic changes are those of typical tubercle formation together with various degrees f caseation necrosis. The structure is largely sar coidal and centers about the horizontal network of blood vessels in the superficial cutis. Tuberculin reactivity is generally negative unless lymph node o systemic tuberculosis is also present. On the basi of 15 cases, Ockuly and Montgomery delineated a form of tuberculosis they believed to be distinct from miliary disseminated tuberculosis and from sarcoid, to be differentiated clinically from lichen planus, lichen nitidus and purpura. While frequently associated with lymph node or systemic disease, the cutaneous condition is essentially benign and pparently responds well to treatment with gold sodium thiosulfate and to isoniazide.

Hematogenous Tuberculosis in the Negro often takes a characteristic configuration, with groups of elastic miliary lesions symmetrically disposed on the eyelids about the eyes, and on the lips chin and ears (Bloom and Mendelsohn ADS 36 937 1937) The trunk buttocks and arms are also likely to show these papules Some cases manifest necrosis and high sensitivity to tuberculin (Irgang ADS 47 627 1943) An occasional patient shows micropapules first appearing on the face but becoming generalized except on volar skin and about the mouth (Irgang ADS 53 372 1946) The facial lesions, when papulonecrotic may closely simulate acne (Irgang ADS 49 351 1944) Various manifestations of skin tuberculosis in the Negro were described by Kennedy et al (SouthMJ 35 449 1942)

See Irgang (ADS 57: 184, 1948); Bernstein (AmJDisChild 57 1260 1939); Alden and Jones (SouthMJ 32 256 1939) dynamic concept of variations of skin tuberculosis.

Tuberculosis Cutis Indurativa includes erythema induratum and similar clinical groups of tuberculous disease in which occur scattered nodular lesions, sometimes ulcerative, the microscope revealing caseating tuberculosis.

Nodular Tuberculosis of the Hypoderm.—Painful subcutaneous nodules of from pea to walnut size were observed in the tissues of the face where they underwent spontaneous involution and caused deeply seated scars, reported Wende (JCutDis 29 1 1911) Animal inoculations from the lesions proved positive.

Erythema Induratum (Bazin s Disease) is characterized by the development of symmetrical indurated cutaneous nodules which terminate in absorption or necrosis. The patients are often girls or women with chilblain circulation. The lesions develop insidiously They are usually confined to the legs, particularly the calves, and the lower third of the thighs. The nodules develop in the panniculus adiposus and first become apparent to the touch as rounded or oval, pea to cherry size, indurated masses which are slightly tender on pressure *and tightly adherent to the overlying skin which* assumes a reddish or purplish hue Many undergo spontaneous involution, leaving discolored, reddish or brownish spots which persist. The mass may ulcerate but necrosis is circumscribed as a rule, and the process is comparatively superficial Tuberculous erythema nodosum (q v) seems to represent more successful immunologic reactivity to bacteria than erythema induratum does.

Nodular Vasculitis.—O Leary (ADS 50 212 1944) described an erythema *induratum like disease productive of scarring* lesions in 3 middle-aged women. Montgomery et al. (J 128 335 1945) reviewed 175 cases of nodular sometimes ulcerative lesions of the legs and 40 cases of recurrent idiopathic thrombophlebitis. While histologic structure suggesting tuberculosis may prove a false suggestion, yet tuberculous disease proved by animal inoculation may manifest only nonspecific inflammatory reaction they pointed out. Diagnosis of tuberculous nodules was accepted if guinea pig inoculation was positive, histologic structure was classic tuberculosis elsewhere in the body was demonstrable by roentgenologic findings or strongly positive tuberculin reaction, and the clinical *appearance and course after prolonged* observation were typical. Among their distinctions, which were argued as not valid by Anderson (J 128 1249 1945) they thought nodular vasculitis more painful than erythema induratum, which occurs in younger women. One of their patients originally said to have a case of nodular vasculitis, did develop tuberculous cervical adenitis illustrating the diagnostic difficulty

The syndrome was accepted by Woodburne and Philpott (ADS 60 294 1949) who thought it may be related to periarteritis nodosa or possibly to panniculitis. The poor circulation in thrombophlebitis leads to enhancement of allergic reaction *within the ill nourished* inflamed tissues, setting up a

vicious cycle explained Nakle (AIntM 80 388 1947) A relation to idiopathic thrombophlebitis as described by Barker (AIntM 58 147 1936) can be imagined.





Fig. 413.—Erythema induratum. (Dr Gustav Riehl.)
Fig. 414.—Erythema induratum. (Drs. Fordyce and MacKee.)



Fig 415.—Sarcoid of Darier Roussy d ... ulcerated, necrotic lesions (Drs. Fordyce and MacKee.)

The debatable status of nodular vasculitis serves to emphasize the facts that some lumps in legs are not tuberculosis and that diagnosis should be critical even if difficult. The condition was considered to be a nontuberculous

type of erythema induratum by Irgang whose 2 cases involved the lower extremities of Negro women with high blood pressure His histologic findings were typical, revealing fat necrosis fibrosis and inflammatory infiltration which included some giant cells.

The scrofulous association of Bazin s syndrome was questioned because of failure to recover the bacillus, not achieved until long after Bazin s first description (in 1858) by Audry in 1898 and by Galloway (BJD 11 206 1899 25 217 1913) noted Wilkinson (BJD 66 201 1954) who preferred the name Whitfield s erythema induratum also championed by Bettley (ProcRoySocM 43 391, 1950) Wilkinson discussed 42 patients with nodular eruptions of the legs showing histologically predominantly vascular changes. They occurred in association with the action of cold in (a) young women who tended to obesity but were otherwise healthy (b) young to middle-aged women with legs affected by poliomyelitis, rheumatoid arthritis or other immobilizing disease and (c) women, not necessarily obese at menopausal age who previously suffered from chilblains, acrocyanosis or Raynaud s phenomenon. Cold alone appeared to be the only cause in 15 of Wilkinson s patients and these he regarded as a nodular form of erythrocyanosis. A few cases mostly males, had nodular eruptions associated with thrombophlebitis or erythema nodosum like eruptions over a number of years and eventually developed arterial disease

Granulomatosis Disciformis Chronica et Progressiva.—Lesions of dubious classification but seeming to possess some relation with erythema induratum were given this name by Miescher and Leder (Dermatologica 9 : 25, 1948) Anterior leg lesions were seen gradually to enlarge with shallow infiltration, raised borders central atrophy and tuberose surfaces. The histologic structure resembled tuberculosis without necrosis. A similar case was described by Wells and Goldsmith (BJD 63: 364, 1951), who referred to 9 cases of Mali (Dermatologica 101: 84, 1950) and a curious morphealike lesio microscopically tuberculous, seen by Goldsmith (BJD 41 226 1929) Nine cases were reviewed by Arzt (Hautarzt 3: 488 1952), who described the disease as occurring usually on the legs but sometimes on the forehead and dorsa of hands and consisting of slightly elevated nummular or annular patches surrounded by an erythematous halo. Histologically he described the dermal infiltrate consisting of circumscribed masses of lymphocytes, rare plasma and giant cells and some epithelioid fibroblasts, and he noted thickening of the walls of the small vessels. In differential diagnosis, one must consider necrobiosis lipoidica, granuloma an ulare morphea and atypical tuberculosis, of which this may be one variant.

Tuberculous Gumma.—Subcutaneous, caseating tuberculosis in the cutis or subcutis develops independently of underlying lymph nodes invades the superjacent skin and eventually ulcerates The names *scrofuloderma gummosa* and *tuberculosis cutis colliquativa* are descriptive (Michelson ADS 10 565 1924) The breast was the site in the case of Garb (ADS 58 308 1948) and Promin jelly cured by local application. Ulceration of the lesions of erythema induratum relapsing after calciferol treatment, produced analogous ulcers (Meer BJD 62 19 1950) Subcutaneous abscesses were featured in a patient of Montgomery (MClinNoAm 19 611 1935)

Unusual Tuberculodermas occur and mixed cases are common. Both the usual forms and the unusual are fairly well comprehended if one keeps in mind the possibilities which may result from variations in virulence of organisms and in responsiveness of the tissues of the host. Sarcoidal structure results from comparatively good immunity (positive hypoergy) and necrosis results from high reactivity (allergy) or from damage by virulent bacteria (negative hypoergy) The multiformity of syphilis scarcely exceeds that of tuberculosis (Montgomery MCNAm 19 611 1935; Blumenthal ADS 35 1037 1937)

Treatment of Disseminated Tuberculosis of the Skin is simply the treatment of active tuberculous disease. Streptomycin yielded dramatic cures in 2 cases of erythema induratum reported by Witherspoon and Hamilton (ADS 64 49 1951) and the effects of streptomycin and isoniazide together in 10

cases were gratifying to Pasleczny (ADS 70 514 1954) One may use vitamin D and isoniazide as discussed under treatment of lupus vulgaris.

Tuberculids.—The term tuberculid indicates, and should be restricted to an eruption due to a shower of tubercle bacilli reaching the skin by embo-





Figs 416 and 417—Tuberculous gummas. (Dr D E. H. Cleveland.)

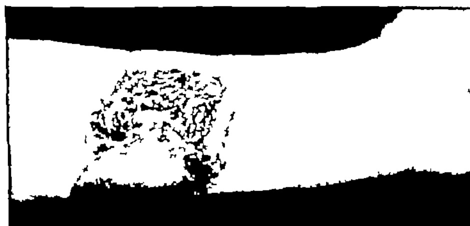


Fig. 418—Tuberculous gumma of forearm. (Dr Sam D. [illegible])

lism in persons with high tuberculous allergy said Rothman (ADS 54 231 1946) Lichen scrofulosus, papulonecrotic tuberculid, and erythema induratum conform with this definition. I see no cogent semantic reason for excluding other eruptions, including those which are sarcoidal presumably

because of positive anergy if they are due to showers of tubercle bacilli also The following descriptions fit certain varieties of tuberculous manifestations.

Hyperergic Tuberculids.—Such doses as 0 1 cc. of 1 1 000 000 dilution of tuberculin result in reactions when injected intracutaneously in certain persons. The conception of hyperergic tuberculids is based on the existence of such sensitivity (Low EdinMJ 39 154 1932)



Fig. 419 —Papulonecrotic tuberculid active lesions and scars. (Drs. Fordyce and MacKee.)



Fig. 420 —Papulonecrotic tuberculid atrophic scarring. (Drs. Fordyce and MacKee.)



Fig. 421 —Lichen scrofulosorum. (Dr T C. Gilchrist.)

These eruptions are thought to be due to multiple emboli of bacilli of low virulence which rapidly succumb in the tissues. Clinical manifestations depend on amount and distribution of the antigen and reactivity of the skin. *Eruptions are better called true tuberculosis if organisms are demonstrable* in the lesions microscopically or by animal inoculation. Tuberculid implies absence of demonstrable organisms occurrence in phthisical subjects *histologic* resemblance to the histopathology of tuberculosis and perhaps, as in lichen scrofulosorum experimental production of the disease by injection of tuberculin. Tuberculous disease in the skin may be divided into (1) true *tuberculosis* (2) tuberculids, and (3) sarcoid forms. In true tuberculosis,

there is classic tubercle formation, caseation occurs, organisms are present and reactivity is hyperergic In tuberculids, there is typical tubercle formation histologically and reactivity is hyperergic but organisms are not present. In sarcoid forms, the tubercle is naked (epithelioid structure) organisms are lacking and the reactivity is hypoergic even anergic.

Lichen Scrofulosorum is characterized by the occurrence of asymptomatic groups of pinhead size pinkish or reddish desquamating papules. The lesions are little, conical papules, which tend to form rounded, superficial plaques, which ultimately disappear without scar The site of predilection is the trunk. The lesions have appeared following injections of tuberculin. Reactivity to tuberculin is high. Demonstrable bacteria are absent. The lesions generally disappear under appropriate treatment Phlyctenular keratitis is an occasional complication. Lichen scrofulosus appeared in conjunction with calciferol intoxication in a case of lupus vulgaris reported by Laden (ADS 57 302, 1948) Cod liver oil is the time-honored medication for this eruption.

Papulonecrotic Tuberculid is manifested with small, discrete lesions of widespread, generally symmetric distribution. They appear in crops and are apparently due to the dissemination of tuberculous antigen via the blood stream Since animal inoculations are regularly negative, the antigenic substance may be either enfeebled circulating bacteria or bacteria killed in the tissues, where they are not to be found microscopically The tuberculin test is positive in extreme dilution. The individual lesions are of various sizes, but are always small. They begin as tiny papules, which enlarge slightly become somewhat tender undergo central necrosis with sloughing or crusting and eventually heal with the production of circular, sharply demarcated scars, which are white, atrophic and slightly depressed. Extensor surfaces of the extremities are the sites of predilection. Itching is absent a distinction from prurigo Compare multiple disseminated tuberculosis of the skin, with reference especially to hematogenous tuberculosis in the Negro.

See Wlassics (DMtsch 76 201 1937), Poor' type, red papules, necrotic centers, healing with central depigmentation; Krantz (ArDuS 178 668, 1938), lesions of remarkable size Parkin (ADS 65 610 1952) appearance during calciferol treatment of lupus vulgaris Pautrier and Weringer (BSocfrançD 46: 412, 1939)

SARCOID

The lesions of sarcoid are typically composed of epithelioid cells, but giant cells, caseation and tubercle bacilli are wanting Since organisms are not ordinarily demonstrable doubt exists as to the specificity of the cause and there is justification for believing that several etiologic agents are capable of provoking sarcoidal tissue reaction. Lesions resembling sarcoid can be caused by leprosy syphilis actinomycosis, trichophytosis, leishmaniasis, lymphoblastoma, and the intradermal injection of foreign bodies, wrote Irgang (ADS 40 35 1939) A sarcoidal rash on the arm of a woman who had previously had *pleurisy with effusion was cured with penicillin*, reported Bernstein and Leider (JID 15 75 1950)

The term sarcoid has been applied rather loosely to a number of chronic granulomatous lesions, wrote Jordan and Osborne (ADS 25 663 1937) They gave a clinical classification (1) miliary lupoid type with small, disseminated nodules, frequently associated with lymph node enlargement often undergoing necrosis and commonly associated with demonstrable tuberculosis elsewhere (2) the deeply seated type of Darier and Roussy and (3) the type to be called Besnier Boeck s disease characterized in its dermatologic aspects by lesions of Boeck s sarcoid or of lupus pernio (q v) and representative of a generalized reticuloendotheliosis characterized by lymphadenopathy and lesions of the same histologic structure in lungs, bone marrow nasal mucosa ocular lacrimal and salivary tissues, liver and spleen.

Boeck s Sarcoid.—Boeck (JCutDis 17 543 1899) described a policeman aged 36 in 1894 whose eruption began on the brow spread t other parts of the face thence to the scalp, trunk and limbs. He was a pale, thin man with groups of lymph nodes much swollen and a

slight increase of wh te blood cells, showing a widespread, somewhat symmetric eruption of firm nodules of varying size on the head and extensor surfaces of the trunk and extremities. The early nodules were red becoming darker and finally yellowish or brown. There was a tendency to peripheral spread and central depression and while some atrophy attended their involution, exudation and ulceration never took place Some lesions on the thigh resembled lichen planus (compare lichenoid tuberculid) This man died from metastases of hyper nephroma in 1940 when he showed only slight, spotty scarlike alteration of the skin of the forehead and temples No sarcoidosis was demonstrable at autopsy but the Kveim test was positive when done in 1940 many years after the disappearance of his sarcoidal skin lesions (Danbolt: SchweizMWehn 77: 1149 1947)

Lupus Pernio of Tenneson (BsocfrançD 3: 4 1 1892) and Besnier (Anndel) 10: 333, 1889) may be considered a variant of Boeck's sarcoid. It was included with cases of multiple benign sarcoid by Jordon and Osborne (ADS 35: 663 1937) and by others, as comprising simply a part of the connotation of Besnier Boeck's disease.



Fig. 422.—Lupus pernio Boeck disease. (Dr Gusta Riehl.)
Fig. 423.—Boeck sarcoid. (Dr J Lamar Callowa.)

As originally described, there occur livid red or purplish, congested lesions on the face nose ears, hands and feet symmetric in distribution infiltrative fairly soft more or less sharply demarcated and differing from true chilblain, persisting throughout the summer Telangiectases are often present Diascopy may reveal minute tubercles Swelling may cause the fingers to become misshapen and ulceration may take place The histologic structure is sarcoidal, yet the disease often associated with lupus vulgaris. Chilblain lupus of Hutchinson (BMJ 1 6, 58, 113 1888) is actually lupus erythematosus and should be distinguished from perniolike tuberculosis of the skin.

See Martenstein (AfDuS 147 70, 1924) Low (EdinMJ 39 189 1932) Kissmeyer and Nielsen (ActaD-V 14 283, 1933), similarity of sarcoid to leprosy review of 200 cases Sulzberger (AmRevTuberc 28 734 1933) classification and quantitative tuberculin tests, Pautrier (PresseMéd 43 148, 1935) multiple benign sarcoid as a systemic reticuloendothelial disease Fulbo (J 105 1205, 1935), simulation by leprosy Ellit (BMJ 2 514, 193), review of enlarging concept of Besnier Boeck Schaumann disease Kreibech in 1904 observed ray changes in hands and feet in lupus pernio, and Jüngling (FortschrGebRoentg 2 375 1920 Delt klin Chl 143 401 1928) recognized osteitis tuberculosa multiplex cystica as being the same.

Subcutaneous Sarcoid of Darier and Roussy (AmédExper 18 1 1906) is rare lial cal form. The lesions are few in number and gradual in evolution, becoming rounded or

ovoid tumors of from 1 to 3 or 4 cm. in diameter Painless, nonulcerative, and located usually in the extremities of women, they resemble the lesions of erythema induratum. Finnerud (ADS 4: 34-, 1921) studied with care a female with mixed manifestations, finding sarcoidal bone involvement but not tuberculous disease. Nodular tuberculosis of the hypoderm is distinguished from sarcoid of Darier-Roussy by the fact that tubercle bacilli are readily demonstrable in the former according to Maloney and Combes (ADS 33: 709 1936) The syndrome may properly be included within the connotation of sarcoid as now understood.

Angiolupoid of Brocq and Pautrier (AnndD 4: 1 1913) has occurred in middle-aged women with sarcoidal lesions sparse in number sometimes solitary on the face, especially on the sides of the nose near the inner canthus The tumors are softly infiltrated, reddish violet in color sometimes streaked with yellow with smooth and telangiectatic surfaces. The distinction of this form from Boeck's sarcoid and miliary lupoid is said to be clear by Auckland (BJD 62: 78 1930) who reported 2 cases and reviewed the literature The lesions are noncaseating tuberculin reactivity is usually present and may be highly sensitive animal inoculations fail and organisms are not demonstrable. The course is chronic, benign and recalcitrant. Local destruction may be required but one of Auckland patients responded well to calciferol.

Sarcoidal Osteitis.—See p. 141.





Figs. 424 425 and 426.—Schaumann disease. A woman from Missouri, whose family lost several members with tuberculosis In the neck were nodules, cystic abscesses and sinuses The skin showed discrete, coppery scaling, infiltrated lesions forming large plaques, resembling the lichenoid tuberculid Photomicrograph illustrates noncaseating epitheloid structure of biopsy from the leg.

Sarcoid in the Skin is characterized by the presence of few or several sharply defined elastic brownish, intracutaneous and subcutaneous nodules which are asymmetrically distributed over the face or extremities or both. The tumors are benign. When they undergo involution, either spontaneously or as a result of therapy they may leave no trace or a pigmented spot or a thinned atrophic, macular cicatrix Clinical varieties are large nodular small nodular or papular and diffusely infiltrating Cases may be atypical or mixed. The skin tumors may range in number from 1 or 2 to 100 or more. The face is the site of predilection. The lesions usually begin as minute firm

rounded nodules which may appear in crops but develop slowly The surface is covered by a fine network of capillaries. After attaining a size from that of a split pea to that of a walnut and persisting for months or years the growths may undergo regression. They almost never ulcerate. Verrucous and papillomatous lesions were seen in a Negro whose unusual lesions perhaps resulted from the admixture of sarcoid and keloid (Irgang ADS 62 105 1950)

Sarcoid a Systemic Disease.—Schaumann (ActaD-V 2 409, 1922 BJD 48 399 1936) collated evidence that sarcoid may be and generally is a disease of wide dissemination in the lymphohematopoietic system. He applied the name lymphogranulomatosis benigna to cases characterized by (1) lymphadenitis in the neck, axillae or groin, (2) epithelioid tubercles in the tonsils, (3) fusiform swellings of the fingers and toes due to sarcoid within the bone marrow and demonstrable radiographically as cavernliform and osteoporotic lesions and (4) skin lesions at first of the type described above later becoming more like those of lupus pernio but with (5) a possibility that skin lesions might not be present at all

Involvement of internal organs is part of the disease, at times the entirety of it, while the complete syndrome with cutaneous osseous lymphatic and visceral lesions is found in comparatively few patients, the majority of whom manifest pulmonic and lymphatic lesions. A review of 35 cases with 4 necropsies by Reisner (AmRevTuberc 49: 289 1944) is worthy of study Mainly young adults, 30 were Negro and 5 white The lungs were affected at least to some extent in 33 with mild nonproductive cough and minimal physical signs. Chest films revealed (1) diffuse, disseminated small nodules as in hematogenous tuberculosis, or (2) diffuse or local strandlike changes following the bronchovascular markings, or (3) patchy coalescent densities suggestive of conglomerate fibrotic induration, usually associated with types 1 and 2. Lymph nodes were usually discrete, movable nontender and moderate in size. Mediastinal and tracheobronchial enlargement was present in 30 cases, typically with widening of the superior mediastinal shadow and prominence of the root areas, usually bilateral and often symmetric, generally without symptoms o signs.

Thoracic studies of value were recorded by Bernstein and Sussman (Radiol 44 37 1945) Pulmonary changes usually started with diffuse infiltration accompanying or soon following bilateral hilar lymph node enlargement. This ranged from a fine miliary type to a coarse, irregular mottling and in half the cases cleared completely eventually When infiltration was progressive, coarse strands in the middle zones evolved, and secondary emphysema often developed (Scadding: BMJ 1: 745 1950) An intensive study of 212 primarily pulmonary cases of sarcoid was presented by Lofgren and Lundback (ActaMScand 14.: 424 1952) The lesions in their patients generally regressed within a year Extrapulmonary lesions were observed in 12% of the cases, those in the skin in 6 instances apparently localized by trauma. Only 1 patient had demonstrable tuberculosis.

Reviewing the Army Institute of Pathology material with 300 cases diagnosed during life and 22 in which sarcoid was found at autopsy Ricker and Clark (AmJCP 19 725 1949) found that the peak age incidence was 20 24 years and Negroes were 17 times as frequently affected as whites. Lymph node enlargement cough, weight loss, skin lesions, low fever malaise and weakness were, in that order of frequency the presenting symptoms. The organs i volved were, in order of frequency lymph nodes, lungs skin, bone, eyes, liver and spleen. Of 88 tuberculin tests, 83 were negative. Hyperproteinemia in excess of 8.0 gm. per 100 cc. was present in only one-third of the cases. See Nelson (AmJMedSci 226: 131 1953)

Infants and children are subject to the disease, although uncommonly A child of 3 months came to autopsy (Nauman ZtschrKinderh 60 1 1938) The course in children is the same as in adults, with widespread systemic involvement, eosinophilia, monocytosis, increase of globulin and reversal of the A/G ratio (Reeves et al. SouthMJ 41: 295, 1948)

Osseous changes, demonstrable in th smaller long bones, particularly the digits and ribs, are sometimes those of osteitis fibrosa cystica, and are found in perhaps a fourth of the cases (Connolly BJRadiol 11 25 1938) Of 63 patients with sarcoidosis, only 11 had bony lesions in the series of H lt and Owens (Radiol 53 11 1949) Diffuse coarse, reticular bone destruct on resulted in a lacelike appeara ce which was more characteristic, they thought, than the circumscribed, punched out foci f Jüngling Differentiation from cystic tuberculous osteitis was discussed by Ellis (InternatCli 4 155 1935)

Myocardial lesions occurred in the patient of Cotter (AIntM 64: 286, 1939) Six cases with cardiac involvement were reported by Longcope and Fisher (ActaM 108: 529 1941) and 15 were collated by Sales (FlaMAJ 40 27 1953) whose original patient died as a direct result of sarcoidal heart disease See Gilg (ActaD V 33 318 1953)

Renal and retinal damage featured the unusual case f Klinefelter and Salley (BullJHH 79 333 1946) Albuminuria, reduced kidney function, and normal blood pressure were noted in 2 cases with renal lesions reported by Ustvedt (abs J 113 1084, 1939)

That uveoparotid fever is a manifestation of Boeck sarcoid was convincingly argued by Longcope and Pierson (BullJHH 60 223 1937) and confirmed by others, including With (AOphth 15 104 1937) and Thompson (AIntM 59 646 1937) Compare Cat scratch d sease.

Uveoparotitis and Mikulicz syndrome are sometimes sarcoidal, believed Pinner (Am RevTuberc 3 : 690 1938) In uveoparotid fever inflammation of the iris and of the parotid glands may develop quickly or slowly Sometimes the onset is febrile with malaise and a toxic rash perhaps resembling erythema nodosum or urticaria is found especially on the lower extremities. The parotid glands generally enlarge at about the same time, causing swelling in the preauricular region with uneven, nodular induration but with little tenderness or pain Other salivary glands may be affected, and dryness of the mouth is a feature Parotid swelling last fo several months and recedes without suppuration. Facial nerve palsy resolving in a few months or a year complicates in about a third of the cases.

Lymphadenopathy is likely to accompany the disease and chest films may yield diagnostically important findings.

Neural symptoms are mostly of the peripheral neuritic type but the central nervous system sometimes suffers from sarcoid (Jefferson: BMJ 2: 916 1932) Pituitary damage in the patient of Barber (BJD 58: 70 1946) caused changes simulating Simmonds's disease and was alleviated by implants of desoxycorticoste one and testosterone. Neural involvement caused Adie s syndrome in a woman who later devel ped uveoparotitis (Lewis BMJ 1: 552, 1941)

Ocular lesions may appear at any time in the course of the parotil anl lymph node manifestations and may undergo resolutions and relapses (Walsh: AOphth 21: 4 1, 1939) Ocular symptoms are generally bilateral and not pathognomonic. Burning, photophobia and misty vision are the complaints, and iridocyclitis is the commonest symptom (Michelson: ADS 39 329 1939) Irregula pupils, keratitis, vitreous opacities and optic neuritis may occur (Cohen and Rabinowitz: J 105: 496, 1935) Eyelids may display millet seed lesions; the lacrimal gland may undergo painless swelling; small sarcoidal lesions may rarely occur in the conjunctiva and episclera; the corneal lesions are generally associated with uveal sarcoid; the most frequent and serious manifestation is nodular iritis and the retina is only occasionally affected (Woods: TransAmAcadOphth 53: 333, 1949)

Etiology.—The cause of sarcoid is not known (Rostenberg ADS 64 385 1951) The relationship to tuberculosis is suggestive but dubious. The tuberculin test in sarcoid is generally negative despite failure to escape tuberculous infection (Bjornstad abs J 144 1130 1950) and this has been thought to signify positive anergy

Tuberculin reactivity was transferred passively using viable leukocytes, as successfully to patients with sarcoid as to tuberculin-negative controls ly Urba h et al. (NEngJM 247 794 1952) Anergy of the sarcoid patients was judged therefore to be nonspecific, since their skins exhibited no inhibition to the transfer Inoculations with living BCG organisms and other antigens were made in 13 patient with sarcoidosis and 11 controls by Rostenberg et al. (ADS 67: 306, 1953) who found no differences in reactivity between patients w th sarcoid and without it. They judged the hypothesis of positive anergy erroneous and that of tuberculous etiology unlikely to be correct.

The problematic coexistence f sarcoid, tuberculin negativity and calcified hilar nodes was explained on the basis of variations in virulence by Kalkoff (abs J 144: 966, 1950) who pointed to the fact that clinical transition of sarcoid into tuberculosis with positive sputum sometimes appears to take place.

Guinea pig inoculations are almost invariably negative until late when the patient may eventually succumb to active tuberculosis. Schaumann (1936) despite extensive inoculation experiments was unable to cultivate the tubercle bacillus from his patients, although 4 of them came to autopsy Schaumann and Hallberg (abs YBD 1941, p. 487) were able to find tubercle bacteria in the tissues w th Hallberg's staining method. Cameron and Dawson (Edin MJ 53: 465 1946) supported the theory of tuberculous etiology with their case. Of 27 cases long watched by Reimer 13 regressed, 9 progressed, and 5 remained stationary He believed the outlook dependent largely on the extent of permanent functional damage of the organs involved, while frank tuberculosis accounts for most of the fatal ties. Efforts to demonstrate *M. tuberculosis* in 17 Mayo Clinic cases failed (Kelman et al: MinnM 32 989 1949) nor could it be found by Doepfmer (DeutschMWchs 78 873 1953) The relationship to erythema nodosum, which occurs in about one-fourth of sarcoid patients, seemed significant to Kerley (BJRadiol 16 199 1943)

A virus resembling that which causes mumps has been isolated from several cases of sarcoid by Lofgren and Lundback (ActaM 138 71, 1950 WienklinWchs 63: 398, 1951)

Pathology.—The nodules consist of sharply defined collections of epithelioid cells with pale-staining nuclei the masses being separated by connective tissue septa within the meshes of which there may occur few giant cells and lymphocytes. The nodules contain vessels, but no elastic tissue The epitheli oid infiltration is the same in the skin tracheobronchial nodes, lungs, bones and viscera. In the giant cells one may find curious asteroid bodies (Lever and Freiman ADS 57 639 1948)

Fig. 427.—Sarcoid, bone changes: cystic lesions as of Jüngling's disease, occurring in patient with cutaneous tuberculosis. Cystic tuberculous osteitis is easily confused with sarcoidal osteitis. (Dr. F. A. Ellis, Univ. of Maryland. Internat. Clin. series 48, 4: 186, 1938.)



Fig. 428.—Sarcoid of Boeck. Classic multiple, loose-set, discrete collections of epithelioid cells. Giant cells scarce. No caseation. (Dr. Fred Weidman.)

Plasma globulin is often increased in sarcoid (Salvesen, 1935 confirmed by Longcope J 117 1321 1941) Hyperproteinemia due to increase of globulin returns toward normal as the patient improves, and is of prognostic significance (Fisher and Davis BullJHH 71 364 1942)

Blood chemical studies showed significant changes in the serum calcium, phosphorus nitrogen and globulin reported Grekin and Curtl (JID 11: 299 1948) Blood changes were reviewed by Jirsebl and Howe (Blood 5 478, 1950) In their study of a patient who had thrombocytopenic purpura due to sarcoid and recovered following splenectomy Anemia, they concluded, is uncommon; polycythemia has occurred; the leukocyte count is generally normal or not far from normal but leukopenia is more frequently found than leukocytosis.

Diagnosis.—As a diagnostic problem the multiformity of sarcoid is such that the patient may present symptoms in almost any specialty the pathologist holding the final decision (Gifford and Krause AOphth 41 667 1949) Diagnosis by needle biopsy of the spleen was reported by Block (J 149 748 1952) Examination of the eyes is indicated in all cases of sarcoid (Dressler and Wagner ActaDV 22 511 1942) for they are involved in about a third of the cases. Confusion is possible with tuberculosis syphilis leprosy lymphoblastomas and other neoplasms, silicosis and berylliosis. Hyperparathyroidism causes general not local decalcification while in sarcoid the serum phosphatase is usually normal and serum protein raised (Salmon and Mynell BMJ 2 1440 1951)

THE KVEIM TEST (REACTION).—Sarcoidal lymph node tissue, crushed under aseptic conditions, mixed with saline diluted 1:10 and filtered through gauze sterilized at 60° C. for 2 hours and tested for sterility by aerobic and anaerobic culture and guinea pig inoculation, is phenolated (0.5%) and serves as the antigen (Danbolt: ActaMScand 114 143 1943) One inject 0.1 to 0.2 cc intracutaneously and observes the test site for several months. Positive reaction is indicated by the development after about two weeks, of persisting erythema and induration, reaching its maximum in two months then fading slowly (Leider: JID 10 377 1948) The positive test site shows sarcoidal structure histologically The test is usually positive in persons with active sarcoidal disease and negative in healed or inactive cases (Nelson: JID 10: 15, 1948) It may have prognostic as well as diagnostic value. Patients with positive Kveim reactions showed a sarcoidal response to intradermal injections of normal splenic tissue (Nelson: ADS 60: 377 1949) The Kveim test is negative in leprosy and the lepromin test is negative in sarcoid according to Wade (JID 17 337 1951)

See Kveim (NordiskM 9 169 1941); Putkonen (ActaDV 23 Suppl 10, 1943 23 391, 1943); Danbolt (ActaDV 28 151 1948) antigen serum protein-linked, heat-stable, destroyed by NaOH Id. (ActaDV 31 184, 1951) specificity Siltzbach and Ehrlich (AmJMed 16: 790, 1954) the Nickerson Kveim reaction a useful confirmatory diagnostic tool, Rogers and Haserick (JID 23 389, 1954) reliable, practical diagnostic aid, Jones and Thomson (QuartJM 24 49 1955) Kveim test provides histologic proof of sarcoidosis, indices of activity progress and value of treatment.

Treatment.—X ray therapy will bring about resolution of the skin lesions as a rule small doses suffice. X ray did not help the lymph node involvement in cases of McCort et al. (AIntM 80 293 1947) Old reports recommended arsenicals intravenously and cod-liver oil was given. Chaulmoogra oil, 3 to 9 cc. intramuscularly each week was recommended by Ormsby (ADS 50 61 1944) Old tuberculin may help when started with 0 1 cc. of 1 1 000 000 gradually increasing the dose at 2 to 3 week intervals.

Calciferol therapy given as for other forms of tuberculosis, induced marked improvement in 2 cases of Curtis et al. (JID 9 131 1947) increased excretion of phosphorus was noted and toxic symptoms developed. Similarly a patient of Robertson (BMJ 2 1059 1948) given vitamin D did not show much improvement until severe intoxication developed but Nelson (JID 13 81, 1949) thought calciferol of little virtue. BCG vaccination helped the 4 patients in whom it took, reported Cornbleet (ADS 62 697 1950)

The influence of hormones was observed by Berman (J 147 246 1951) whose patient was much better during each of 2 pregnancies. Cortisone yields remarkable results (Ronchese and Schiff ADS 64 806 1951); see Siltzbach et al., Lovelock and Stone and Small (J 147 927 930 932, 1951) whose patients collectively had ocular pulmonary cutaneous and lymph node involvement, all of which showed dramatic improvement on cortisone Some patients hold their remission and others relapse more or less promptly after with

drawal of the drug (Shulman et al. BullJHH 91 371 1952) An ocular case exhibited remarkable recovery of vision, and 12 other patients with sarcoid made various degrees of recovery on doses of from 100 to 150 mg per day given by Siltzbach (AmJM 12 139 1952) In ocular cases, it must be given early if vision is to be saved (Dolphin and Heathfield Lancet 2 1160, 1952) The benefits from cortisone are most striking upon extrapulmonary *manifestations and in patients with symptoms of brief* duration, the effects being less in pulmonary infiltration and little in mediastinal lymphadenopathy according to Israel and Harrell (J 156 461 1954) They felt that the course of the disease over the long term was favorably influenced in only the minority of cases and 4 of their 36 patients died of sarcoidosis in spite of cortisone therapy

Local infiltration of the individual skin lesions with hydrocortisone acetate produced nearly complete resolution with subsequent partial relapse observed Sullivan et al. (J 152 308 1953) They found that cortisone by mouth was likewise palliative *only while it was given. Palliation may be most gratifying to a patient* who without cortisone would be desperately ill (Dent et al BMJ 2 808 1953) That cortisone aggravates the process was denied by Lovelock and Stone (AmJMed 15 468 477 1953 J 169 69 1955)

Isoniazide may produce some benefit and being almost harmless is worth a trial It helped 2 of the 6 patients of Edelson (JID 21 71 1953), p 339

See Salvesen (ActaM 86 127, 1935) 4 systemic cases, Hunter (NEngJM 214 346, 1936), systemic manifestations Mellon and Helmhauer (ADS 36 315, 1937 37 451, 1938) etiology in avirulent dissociated forms of tubercle bacillus Nickerson (APath 24 19 1937) 8 autopsies, reticulum not destroyed as it is by tuberculosis Lomholt (ActaD-V 18 131 1937) 40 cases reviewed, half with bone lesions, 90% with intrathoracic Scott (BMJ 2 777 1938), 8 cases, including Heerfordt's uveoparotid syndrome, Spencer and Warren (AIntM 62 285, 1938) autopsy showing myocardial, renal and thyroid lesions Cornbleet and Rattner (ADS 40 211, 1939) 3 cases, Negro Leder (Dermatologica 80, 142, 1939), 13 cases followed for from 3 to 15 years without developing active tuberculosis, Saenz and Palomino (ADS 39 456, 1939) tuberculoid leprosy Lambie (MJAustral 1 815 1940) review Pautrier (La Maladie de Besnier Boeck Schaumann, Masson, 1940) Vorbein and Bonnevi (ActaD-V 21 408, 1940), 34 cases Herrell (AIntM 65 1003, 1940) 11 cases Cameron and Dawson (EdinMJ 49 727 1942) case and review doubts on tuberculous etiology Pakov and Taylor (JLCM 27 1284 1942) histology, Ronchese (ADS 46 800 1942) case, autopsy miliary tuberculosis of lungs, Thornhill (AmJDisChild 64 262, 1942) ocular lesions in child Fletcher (AOtol 39 470, 1944) 4 cases involving septum and turbinates, mechanical symptoms, Bates and Walsh (AnnIntM 29 306, 1948) 7 cases, 1 autopsy Michelson (J 136 1034 1948), review Leitner (Der Morbus Besnier Boeck-Schaumann, Basel, 1949) 318 p. monograph (abs ADS 61 171 1950) favoring tuberculous etiology, Curran and Curran (Surg 28 874, 1950) pancreatic involvement Riley (AmRevTuberc 62 231 1950) 52 Bellevue cases, showing predilection for young Negro adults, mortality about 20% Howles (SouthMJ 43 633, 1950), 43 cases, review Hartweg (DMedWchr 76 1144 1951) 79 cases, lung appears to be portal of entry Simkins (J 146 794, 1951) myocardial involvement Hanes (JKaMS 53 338, 1952), effectiveness of cortisone without which disease is not so benign as alleged Longcope and Freiman (Med 31 1 1952) monographic, 160 cases, cause unknown, multiplicity of symptoms, mechanically damaging Duperrat and Vautier (abs J 151 333 1953) pleuric involvement Rogers and Netherton (J 155 974, 1954) in identical twin Letter from Sweden (J 154 1113, 1954), work of Jörgen Schaumann, who died of coronary thrombosis Aug. 9 1953 Schaumann (AnndeD 80 467 1953) cases with pruritus, prurigo, excoriations, pigmentation and depigmented scars Schlapper (BeitrKlinTuberk 112 83 1954) various manifestations and relationship to eponymic syndromes, case helped by streptomycin Löfgren (abs J 156 1319, 1954) erythema nodosum in sarcoid Löfgren et al. (ActaPaediat 43 Supp 100, 1954) BCG given in 20 pulmonary cases, showing depression of tuberculous sensitivity no positive [illegible] rapid absorption of radioactive BCG in seven cases suggested decreased immunity

LEPROSY

Leprosy is a disease believed to be due to infection with *Mycobacterium leprae* Hansen's bacillus. While Koch's postulates have never been fulfilled (Edit InternatMDig 37 254 1940) this acid fast organism, similar in many respects to *Myco tuberculosis* apparently provokes chronic inflammatory disease of tuberculoid histologic structure with acute exacerbations, or lepra reactions, by altering reactivity and by invading and destroying cutaneous and peripheral nervous structures. Noteworthy similarities exist between leprosy and tuberculosis with respect to chronicity causative organisms, granulomatous and tuberculoid histopathology wide range of clinical manifestations, and dependence of the morbid phenomena on variations of immunity of the host and virulence of the parasite (Johansen AmRevTuberc 35 609 1937) BCG vaccination appears to have a prophylactic influence against the development of leprosy (Schujman InternatJLepr 21 313 1953)

15 cases in British Isles; Fite (BullN tInstH p. 45, 1940) experimental in rat; Loving (JInfectDis 68: 191, 1941) in rabbit; Rogers (Leprosy William Wood & Co., 1940), 240 pp.; Burgess (Who Walk Alone, Holt, 1940) about the people who ha the disease; Burks and Brunsting (PMMC 16 468, 1941) pemphigoid case, bullae for 4 years Faget (PHRpts 57 641 1942) history of National Leprosarium at Carville, La.; Frazier (J 123: 466, 1943); Contreras and Guillen (be J 125: 870, 1944) early diagnosis, Bechelli (JID 6 337 1945) needl puncture test analogue of histamine test Arnold (ADS 52 384, 1945) diagnosis Meiser (LeprRev 16 49 1945) transmission in cockroach; Portugal and Rocha (ADS 53 471 1946), juxta-articular nodes, Fielding (MJAustral 1: 578, 1946), transmission by rats Cochrane (Practical Textbook of Leprosy, Oxford U I Press, 1947) 283 pp.; Muir (I ternat JLepr 15 309 1947) Diasone treatment Chaussinand (InternatJLepr 16 431, 1948) antagonism of tuberculosis and leprosy Metcalf (LSNMJ 48: 668, 1948) contribution of orthopedic surgery in leprosy; Arnold (ADS 60: 1148 1949), immunology and clinical lesions Wade (J 140 1113, 1949) ccidental inoculation; Rosenjamin (InternatJLepr 17: 217, 1949) extirpation of local lesion; Davison (I ternatJLepr 17: 247 1949) neural leprosy is infectious; Simons (IJJD 61 95, 1949) transmission, contagion, accidental inoculation, control Muir (InternatJLepr 18 309 1950), diaminodiphenylsulfone Ryrie (Lancet 2: 230, 1950) mithiosone; Sloan et al. (HawaiiMJ 9, 301 1950) sulfones Vegas et al. (I ternatJLepr 18 451, 1950) amithiozone beneficial, no intolerance Kell (InternatJLepr 19 437 1951), amithiozone Grabstald and Swan (J 149 1287 1952) testicula lesions, atrophy in 28%, many with gynecomastia Gray and Bancroft (InternatJLepr 20 467 1952) 141 of 607 deaths t Carville showed moderate to far-advanced tuberculosis, which was a primary or contributory cause of death in 23% of ll deaths sulfone therapy has reduced leaths more in cases with t berculosis than in cases without it Rogers and Adamson (IDIJ 3: 259 1953) 48 cases notified 1 1951, 65 in 1952 in England and W les, 7 in Scotland through 1952; Wolcott and Ross (InternatJLeprosy 21: 434 1953) exacerbations more common in treated patients since 1948; Innes (LeprosyRev 24: 224, 1953) in African children Letter from Denmark (J 155 299 1954) leprosy in mediev l skeletons from N est ed Levan (J 156 120, 1954), Kansas acqu red leprosy in milit ry service (see Aycock and Gordon, AmJMSci 214 329, 1947); Dreisbach (LeprosyRev 25 81 1954) leprosy in 7-month-old child Rehich (LeprosyRev 25 170, 1954) treatment of t berculosis in leprous patients with isoniazide and streptomycin or PAS, giving iso sulfones or thiosemicarbazone Byers and Wolcott (InternatJLepr 22: 266, 1954) sulfone treatment eliminated M lepra from nasal scrapings in 80% of cases within 1 year from kin scrapings in less than 10% in from 1 to 10 years Bechelli (abs J 157 1244 1955) leprosy in the liver which was enlarged in 30% of 1039 Brazilian cases, lepra reactions causing acute, painful hepatomegaly

GRANULOMA INGUINALE

Granuloma inguinale is a chronic disease due to infection with an encapsulated bacterium, *Donovania granulomatis* affecting primarily the skin and mucous membranes. There is at first a small papule which enlarges, coalesces with adjacent lesions ulcerates and produces a vivid hued, shining verrucose vegetating plaque of granulating tissue with a hemorrhagic surface surrounded by thin, easily excoriated epidermis (V D Committee Rpt J 116 2405 1941) The disease spreads by peripheral extension and autoinoculation so as sometimes to produce extremely extensive lesions, often resembling vegetative carcinoma, from which the distinction is accurately made only by biopsy (Beerman and Sonck: AmJSyph 36 501 1952) MacKay and Bunch (AmJSyph 36 511 1952) observed carcinoma following vulvar granuloma inguinale so that care in diagnosis is essential.

It is exceptional for healing to occur spontaneously if it ever does. The ulcers are superficial with somewhat raised, nodular irregular borders. They give rise to comparatively little pain. There is seldom associated lymphadenitis. Rarely there is seen a lymphangiitic abscess with bubonulus (Sobel and Pensky ADS 48 494 1943) but abscess formation is exceptional. Nodular ulcerovegetative hypertrophic, and cicatricial types are recognized (Haity s classification Pariser and Beerman: AmJMSc 208 547 1944)

Extragenital cases are recognized (Greenblatt et al. ADS 38 358 1938) The lip neck, mouth and elsewhere generally in association with pudendal lesions, are sites which have been involved The incidence of extragenital involvement approximates 6% (Palik and Schenken AmJCP 15 419 1945)

Neonatal infections were reviewed by Scott et al. (AmJDisChild 38, 242, 1953) whose patient had lesions in the postauricular region followed by ulceration of the umbilicus and penis, and the mother s vulvar sore contained Donovan bodies.

The cervix uteri is occasionally the location (Pund and Greenblatt J 108 1401 1937) The upper lip was affected in the case of Hall (ADS 38 245 1938), the eyelid in the case of Weiner et al. (AmJOphth 26 13 1943) the clavicle and ribs in that of Paggi and Hull (AnnIntM 20: 686 1944) Pelvic involvement, including fatal cases, was described by Pund and McInnes (Clin 3 221 1944) malaise weakness, fever anemia and leukocytosis are features. Polyarticular arthritis and osteomyelitis were noted by Lyford et al. (AmJS





Fig. 440.—Granuloma inguinale, with destruction of penis

Fig. 441.—Granuloma inguinale labial ulcerative lesion. (Courtesy of Drs. E. R. Ferro and J. W. Richter from Thoma Oral Pathology ed. 3, Mosby 1950.)



Fig. 442.—Granuloma inguinal of the cervix uteri. (Adams and Packe South MJ 48 27 1955.)

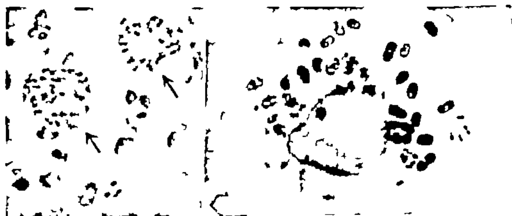


Fig. 443A.—Donovan bodies in large monocytes. (Pund et al. Arch Path 23 224 1937.)

Fig. 443B.—Donovan bodies, Wright stain. (Fox J 87 1785, 1926.)

28 588, 1944) The Negress of Packer et al (J 136 327 1948) had bone metastases and profound systemic manifestations from a cervix primary yet was cured with intravenous antimony

Etiology—Experimentally reproduced infections in human beings were described by Greenblatt et al. (J 113: 1109 1939) The Donovan body was apparently successfully cultivated in the yolk sac as an encapsulated bacterium, *Donovania granulomatis* by Anderson et al. (AmJSyph 29 165 1945 JExpM 81 25 1945) See Cornwall and Peck (ADS 12 613 1925) Success in cultivating the organism on an artificial medium of beef heart infusion broth with some normal egg yolk was obtained by Durham and Rake (AmJSyph 32: 145 1948) A yolk sac culture produced a successful human inoculation, claimed Dienst et al (AmJSyph 31 614 1947); but failure of inoculation with cultured organisms was later reported (AmJSyph 33 152, 1949)

The bacterial behavior of *D granulomatis* was reviewed by Goldberg et al. (AmJSyph 37 60 1953) It appears as nonmotile pleomorphic, gram negative rods, about 0 6 by 2.0 μ in size usually containing granules which are frequently bipolar On Dulaney s medium the organisms were embedded in a matrix of mucoid. No strain could be grown on a medium which did not contain egg yolk or a derivative thereof

Perhaps infection is transmitted by pubic lice (Butts and Olansky: ADS 54 524, 1946)

Diagnosis requires laboratory proof of the presence of the Donovan bodies. The tissue smear method described by Chen et al. (ADS 58 703 1948) is accomplished by selecting a typical red friable bit of granuloma which is cleaned well with a cotton applicator and nipped off with the corners of two slides, obtaining a quantity of perhaps 2 cu mm This is pressed firmly and ground between the slides to obtain a thin smear then the slides are pulled apart and dried. They are stained for 90 seconds with a mixture of 0.5% Wright s stain, 3% glycerol and acetone-free methanol then to this is added an equal amount of distilled water for 3 minutes. After washing and drying Donovan bodies are to be sought in the cytoplasm of the monocytes with the oil immersion lens. The search might be simplified they said, by preliminary use of penicillin or sulfonamide drugs to eliminate other microorganisms. See Cannefax (JVDI 29 201 1948)

A staining method using basic fuchsin 0.5% decolorizing with 0.5% citric acid, washing and counterstaining with 1% aqueous methylene blue was described by Mortara and Dienst (AmJSyph 27: 296, 1943) One may obtain a clean bit of granulation tissue by means of a biopsy punch and smear it as a film; flood the slide with pinacyanole dye 1% in methanol for 90 to 120 seconds, dilute with an equal quantity of neutral water for another 90 to 120 seconds, wash with distilled water and examine (Greenblatt et al. AmJSyph 35 291 1951) The smear must contain intact macrophages sufficient for diagnosis and Wright stain is serviceable (Packer and Dulaney: AmJSyph 33: 63, 1949) Pund and Greenblatt (AP th 23: 224, 1937) demonstrated the presence of true Donovan bodies in their cases with regularity and dependability both in smears and in sections.

Intradermal injection of triturated infected material may yield positive tuberculoid reactions (Kornblith: ADS 60 275 1944) The culture used as antigen gave positive tuberculoid skin reactions, and positive complement fixation tests were reported by Jenson et al. (ADS 55: 324 1947) The complement fixation test is a useful diagnostic tool, according to Goldberg et al. (AmJSyph 37 71, 1953) Skin reactivity to the yolk sac vaccine begins about two weeks after the onset of the infection (Chen et al. AmJSyph 33: 60 1949)

Carcinoma may develop during the course of the disease, or it may simulate granuloma inguinale, in either case introducing a diagnostic problem the solution of which depends on prompt biopsy (Alexander and Shields ADS 67: 395, 1953)

Treatment.—Prior to the availability of effective antibiotics, cures were obtained by the intravenous injection of 5 cc. of 1% aqueous solution of potassium antimony tartrate on alternate days. The drug is likely to provoke vomiting unless given conservatively A dose of 5 cc. of the 1% solution may

be increased 1 cc. at a time to perhaps 10 cc. intravenously Antimony treatment must be persisted with until the lesions are healed. Fuadin a complex trivalent antimony compound, is highly effectual and relatively nontoxic.

Of the many chemotherapeutic agents tried streptomycin in the extremely low concentration of 6 2 gamma per ml. was most effective in protecting the chick embryo (Rake and Dunham Am JSyph 31 610 1947) Streptomycin was found curative in human beings by Barton et al (ADS 56 1 1947) and others. A dose of 0.5 Gm per 6 hours for 2 weeks may be recommended for a total of less than 4 Gm. is likely to be followed by relapse Donovan bodies cannot be found after the fourteenth day and are often gone by the sixth The hazards of eighth nerve damage kidney injury and depression of the bone marrow must be borne in mind when streptomycin is used. Streptomycin, 4 Gm. per day for 5 days is usually adequate wrote Greenblatt et al. (JVDI 28 3 1947) Hirsh and Taggart (AmJSyph 32 159 1948) cured all 21 cases treated with 0 17 Gm. 6 times a day for 6 to 47 days. On 4 Gm. per day for 5 days, 50 of 51 cases were reported cured by Kupperman et al. (J 136 84 1948) Rapid cures with streptomycin were reported by Samitz et al. (JID 12 85 1949) A dose of 4 Gm. per day was recommended by Dienst et al. (UCutRev 51 537 1949) who found that less than 2 Gm. per day is inadequate while Aureomycin proved surprisingly effectual although slightly



Fig 444—Granuloma inguinale *A* before treatment with Chloromycetin *B* aft first course of 20 Gm of Chloromycetin given in 10 days, *C*, after a second, similar course of therapy (Greenblatt et al. AmJObGyn 59 1120 1950 from Crossen Diseases of Women, ed 10 Mosby 1953)

slower All the patients they treated with Chloromycetin were cured and the Donovan bodies disappeared faster than with either streptomycin or Aureomycin. Cases resistant to streptomycin were cured by Aureomycin or Chloromycetin, reported Lariser et al. (ADS 62 251 1950)

Terramycin is also curative (Hendricks et al. J 143 4 1950) The total dose must be 40 Gm. or more, at 1 0 Gm. q.i.d. stated Niedelman et al. (AmJSyph 35 482, 1951) On Terramycin, the Donovan bodies disappear in from 4 to 5 days (Greenblatt et al. JVDI 32 116 1951)

Aureomycin was effective in 5 cases resistant to streptomycin (Greenblatt et al. AmJSyph 33 593 1949) and a total dose of 20 Gm. in 10 days appeared to be the minimal satisfactory schedule The drug was adjudged superior to streptomycin by Hill et al. (J 141 1047 1949) A streptomycin-resistant infection was inoculated into a volunteer in whom also it proved to be streptomycin resistant, but both were cured by Aureomycin, reported Dienst et al. (AmJSyph 34 189 1950) The drug must be continued longer in extensive cases (Wammock et al. JID 14 427 1950)

Chloromycetin seemed superior to Aureomycin in the experience of Robinson and Cronk (AmJSyph 35 378 1951) *Chloromycetin in a total dose of 20 Gm. was excellent and prompt* in the experience of Greenblatt et al. (GaMAJ 38 206 1949) This quantity given at the rate of 0.5 Gm. each 6 hours,

cured 23 female cases either in the first course or the second reported Greenblatt et al. (AmJObGyn 59 1120 1950) The same dose was well tolerated and no relapse occurred in 9 cases of Zises and Smith (AmJSyph 35 294 1951)

Reviewing 295 cases variously treated with antibiotics, Greenblatt et al. (AmJSyph 36 186 1952) judged streptomycin, Aureomycin Terramycin and Chloromycetin all effective. Streptomycin should be given 4 Gm per day for 5 days, but some cases were unresponsive Such cases were responsive to the other drugs, and there was no failure with Terramycin Patients undergoing antibiotic treatment should be hospitalized they believed. Erythromycin, 100 mg q.i.d., cured 8 of 9 cases when given in enteric-coated capsules by Robinson and Cohen (JID 20: 407 1953) Magnamycin appeared curative when tried by Whitaker et al. (AmJSyph 37 466 1953) In doses of 200 to 300 mg q.i.d. it cured all 9 cases of Robinson and Cohen (JID 22 263 1954) Carbomycin gave the best results in the cases involving the cervix reported by Adams and Packer (SouthMJ 48 27 1955)

Penicillin is without effect (Nelson AmJSyph 28 611 1944)

See Donovan (IndMGaz 40, 414 1905); Walker (JMRes 37: 427 1918) culture; Goldzieher and Peck (ADS 14 14, 1926), cultures Cole et al. (DZtschr 83: 177 1928) in U.S.A. Hasera et al. (J 99 1410 1932) antimony treatment Menon and Krishnamani (IndMGaz 68 500 1933) Donovan bodies Haity (AnndeD 4 1101 1933) classification Araga (CompterendSocBiol 114 841, 1933) *C lymmat bacterium granulomatis* DeMonbreun and Goodpasture (JTropM 13 447 1933) failure to cultivate, Nai and Pandalai (IndMGaz 69 361, 1934), history and review; Pund and Greenblatt (APath 23: 224, 1937) diagnosis Cole (PaMJ 40 802, 1937), comparison with lymphopathia venerea; Alexander and Schoch (AmJSyph 24: 180, 1940) Giemsa stains organisms in tissues; Arnell and Patelon (AmJObGyn 39: 626, 1940), worse in pregnancy Robinson et al. (SouthMJ 35 859 1942) surgical treatment Allison (SouthMJ 4 274, 1948) lithium stibiothiomalate an effective trivalent antimonyl; Dienst (AmJSyph 32 301, 1948) diagnosis and cultivation; Greenblatt et al. (SouthMJ 41 1121 1948), Aureomycin; Marshak and Rodriguez (J 137: 1292, 1948), streptomycin; Eisenberg (AmJSyph 32 468, 1948) extragenital; Rake (AmJSyph 32: 150, 1948), antigenic relationship with klebsiella, Spenser (AmJObGyn 56, 1181, 1948) cervix, differentiation of cancer Sauer et al. (WVaMJ 41 18, 1948), streptomycin Thompson et al. (SouthMJ 41, 994 1948), streptomycin; Jacoby et al. (AmJSyph 32 76, 1948) streptomycin Marmell and Santora (AmJSyph 34 83, 1950) diagnosis of "donovanosis

RAT BITE FEVERS
SODOKU AND HAVERHILL FEVER

Two different infections difficult clinically to distinguish from one another may be inoculated by rat bite Sodoku, the usual rat bite fever due to *Spirillum minus* and Haverhill fever due to *Streptobacillus moniliformis* In the spirillar type, the wound becomes inflamed, the regional nodes enlarge and a dark reddish rash may first appear about the bite and then become generalized. In the streptobacillary type, the incubation period is shorter the fever is less regular in its relapses joint pains and arthritis are common and few local inflammatory signs are seen (Brown and Nunemaker BullJHH 70 201 1942)

Sodoku.—*S minus* is a naturally occurring parasite of rats, a short, thick, actively motile organism with tapering ends. Identical with the Japanese *Spirocheta morsus-muris* it has a rigid body moves rapidly with bipolar flagella and is 2 to 5 μ in length, with 3 or 4 waves. After an incubation period of 10 to 40 days, the original wound having healed a nonpurulent inflammation recurs at the scar and lymphangitis and symptoms of general infection develop with intermittent fever of ? to 7-day periodicity Erythematous, indurated plaques develop at the inoculation site and undergo exacerbation with each rise of temperature A satellite bubo is usual, and spirilla may be found here as well as in the chancre on dark field examination. Of 65 cases of rat bite treated at the Johns Hopkins Hospital 10% got the disease 60% were under 1 year of age and none died (Richter J 128 324, 1945) Serologic tests for syphilis become positive in this as in other spirochetoses. The disease followed a cat bite in the patient of Swyer (BMJ 2 386 1945) and was due to the bite of a field mouse in that of Reitzel et al. (J 106 1090 1936) A painless nodule of walnut size with watery discharge and no lymphangitis appeared in the case of Beaumont and Gill (BMJ 1 582, 1935) and the rash,

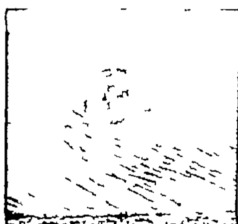
accompanying a fever of 104° F was circinate appearing first on the forehead, then on the face arms and trunk. Diffuse erythema on the outer aspects of the arms and macular blotches over the abdomen were seen by Beeson (J 123 332 1943) Chills and muscle and joint pains underwent paroxysms at intervals of 5 days in the cases of Leadingham (AmJCP 8 333 1938) See Crohn (AIntM 15 1014 1915) 52 cases Blake (JExpM 23 39 1916), 28 more cases Knowles and Das Gupta (IndMGaz 63 493 1928) 28 cases from Calcutta

Sodoku has been used to induce fever in the treatment of syphilis (Rothström: Fi sk. Läkaresk. Handl. 77: 51, 1930)

Diagnosis is established by identifying the organism, which can be done by dark field examination of the chancre and by inoculation of the patient s blood i to mice the peripheral blood of which is examined at daily intervals (Watkins JPed 28: 429 1946)

Penicillin is usually curative (Frank and Perlman ADS 57: 251 1948 Oehme DMedWchn 75 1258 1950) Streptomycin cured an unusual case unresponsive to penicillin reported by Jellison et al. (PHRpts 64: 1661, 1949)

Neoarsphenamine effective in the cases of Chopra et al. (IndMGaz 4 449 1937) and of Gilkey and Dennie (SouthMJ 32 1109 1939) fails in Haverhill fever





Figs 445 and 446.—Sod ku hancre t site f bite showing necrosis nd surrounded by inflammation (Gradwohl et al Clinical Tropical Medici e, Mosby 1951.)

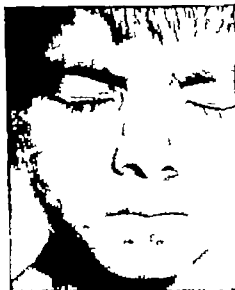
Haverhill Fever (Erythema Arthriticum Epidemicum) an illness recognized in Massachusetts in 1926 (Place and Sutton AIntM 54: 659 1934) is characteri ed by abrupt onset with chills fe er vomiting headache, pains in the back and rthralgia. A macular papular or petechial rash appears early especially on the extensor spects of the extremities. The organism cultivated from the blood was called *Ha erhillia mult formis*, late identified as *Streptobacillus moniliformis*. See Place et al. (BostonM&SJ 194: 285, 1926); Pa ke and Hudson (AmJPath : 33 , 19 6), blood cultures; Hazard and Goodkind (J 90 534, 1932) Rat b te inoculated this disease i the case of Farrell et al. (AIntM 64 1 1939) Of 3 cases of rat bite fev r of Kirkwood and Stoll (IllMJ 80: 141, 1941) were spirilla and 1 streptobacillary In the latter type of infection, the incubation period is brief only 3 to 5 days, the feve falls afte only a few days, and the rash is morb lliform. A secondary feve ppears soon after the first deferv escence is quickly followed by polyarthritis, which may pers st fo weeks or months. Some cases unresponsive to rsenical and antimonyl drugs ha e been known to end re for years, with polyarthritis, severe disability and even fatality (Webe a d Favour BullJHH 77 132, 1945) A fatal case with chro c arthritis and f ver was observed by Morse (SoWM 31: 264, 1950)

Accidental inoculations of laboratory wo k rs have been reported by Levin and Civin (AI tM 80 53 1947) and Lom naki et al. (BMJ 1: 510 1949) Both were promptly cured by penicillin.

Pe icillin is usually gratifyingly effective (Wheele AmJDisChild 69: 215 1945; Alteme er J 127 270 1945; Labensky ConnSMJ 10 557 1946) Streptomycin was thought more effectual than penicillin by Sprecher and Copeland (J 134: 1014, 1947) fo tests in vitro show greater susceptibility as Brookeater (JPe : 442, 1943) observed

PINTA

Pinta is a common disorder of Mexico and Central America characterized by startling depigmentary changes. A disease of interesting and exotic history it was long and erroneously thought mycotic in origin.



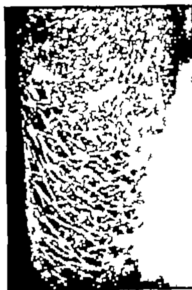


Fig. 447.—Pinta. Blue pigmentation of nose and lips in untreated boy dark-field positive. (Dr Robert Andrade.)

Fig. 448.—Ichthyosiform pintid of leg in untreated boy dark-field positive. (Dr Robert Andrade.)

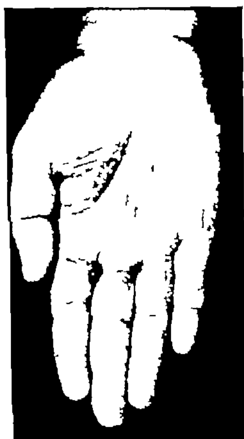




Fig. 449.—Palmar pintid simulating dermatomycosis. (Gradwohl et al. Clinical Tropical Medicine, Mosby 1951.)

Fig. 450.—Papulosquamous pintid, set on extensive erythematous plaque on thigh. (Gradwohl et al. Clinical Tropical Medicine, Mosby 1951.)



Fig. 451.—Pinta. (Dr O G Costa.)
Fig. 452.—Ichthyosiform pintid. (Dr Robert N Andrade.)
Fig. 453.—Bluish gray pigmentation of waist and thigh of 12 year-old boy in whose lesions *T carateum* was demonstrated. (Dr Robert N Andrade.)





Fig. 454.—Pinta. (Pardo-Costello and Ferrer ADS 45 843, 1942.)
Fig. 455.—Pinta. Middle finger close-up is shown in Fig. 451. (Dr O. G Costa.)

On Aug 6, 1938, a treponema was discovered in the serum of scrapings from active lesions by Armenteros and Triana in Saenz s patient in Havana, the organism being demonstrated in lymph nodes and tissues of this patient days late by Leon y Blanco (RevMMex 18: 617 1938) See valuable review of Holcomb (USNMBull 40: 517 1943) and Edit. (J 126: 1030 1944)



Fig. 486.—Volar keratoses of corneous pintid. (Dr O. G. Costa.)





Fig 487.—Pinta. Superficial inflammation simulates that of mild lichenoid dermatitis. (Dr H. A. Gall.)

Fig. 488.—Pinta, showing translocation of pigment into dermal chromatophores. (Dr Howard Fox.)

T carateum is a straight spiral 7 to 15 μ in length with 6 to 1. coils, rigid and regular It occurs in the blue lesions. Leon y Blanco inoculated himself successfully and, with Latapi (Medicina 20 315, 1940, also ADS 46 149, 194.) described early lesions. They accredited Herrejon with having earlie established the spirochetal nature of the disease (VDI 21: 270 1940)

In the experimental disease, a small lenticular papule develops on the seventh day at the site of inoculation. This reaches maximum development within 3 weeks, becoming a scaly flattened, oval plaque 2 to 3 cm. in diameter which remains solitary for 3 to 9

months. The dissemination of a secondary generalized eruption sets in. The lesions are hamlike or slate-colored, superficial and scaly, identical with those of naturally acquired pinta, and are accompanied by the development of positive serologic reactions for syphilis. See Oteiza (abs YBD 1940, p. 561)

When *T carateum* was inoculated into each of 9 patients with yaws and free from syphilis, pinta developed in only (Goncalves abs BJD 50 23 1947 Blanco abs YBD 1947, p. 548) Inoculated into 6 syphilitics, there were 5 failures to take (Oteiza abs BJD 58 107 1946)

The naturally acquired chancre develops in 2 stages (Blanco and Lacoa AmJSyph 31 600 1047) at first resembling an infiltrated papule later becoming an erythematosquamous patch of a size varying with its period of evolution The lentil-sized early papule is visible within 10 days or less, becomes an oval brownish red plaque within a month, either elevated 2 or 3 mm or level with a halo of scales. This becomes a flattened sharply demarcated oval patch somewhat infiltrated pinkish, and furfuraceously scaly If the scales are scraped off the surface is lichenoid. Slow progression ensues with centrifugal expansion and confluence of peripheral lesions. The late primary lesion may be psoriasiform dermatomycotic in appearance or lichenoid The initial lesion occurs on the lower extremities in 80% *of the cases on the upper* extremities in 10% and on the face in 5% Dissemination does not occur earlier than 2 months and may be delayed even several years.

Pintids are erythematosquamous plaques like the primary They appear in crops and do not disappear spontaneously They remain localized or if generalized are not as a rule distributed with symmetry The lesions result in depigmentation On a dark skin, bluish scaly lesions and sharply defined vitiliginous lesions may coexist. Remarkable variation of color is seen, and dyschromic patches are often checkered. Pruritus excoriation and secondary infection may modify the picture

Lymphatic involvement is discrete nontender and syphiloid Melanotic pigment and curious hyaline corpuscles are found in the nodes (Deerman AmJMSci 205 611 1943) Serologic tests become positive in all late cases and are likely to be irreversible. Spinal fluid changes like those of syphilis were found in half of the 41 cases studied by Pardo-Castello and Ferrer (ADS 45 843 1942) and cardiovascular changes in two-thirds of them Neurologic and cardiovascular involvement is fully as significant in pinta as in syphilis. Lieberthal (J 123 619 1942) described cases in the United States with late manifestations

Treatment of pinta is like that of syphilis. Mapharsen and penicillin are effective although dyschromia remains as a rule (Varela and Avila AmJ TropM 27 663 1947)

Following the administration of penicillin *T carateum* disappears from the lesions within 6 hours while other antibiotics produced this change only after a much longer interval of time (Rein et al abs J 148 1452 1952) Serologic response to treatment was slow during the 2 years that 350 cases were under study probably because of the long duration of infection prior to treatment The pintids, too required several months to disappear A single injection of microcrystalline procaine penicillin G in oil with aluminum monostearate is highly effectual (Rein et al JID 18 137 1952)

See M LeRun (EdinM&SJ, 1828) Fox (ADS 18 673 1928 in Columbia 31 337 1933 in Mexico 36 614 1937 39 709 1939, spirochetal etiology reported by Saenz et al) Lroeña et al (Primer Censo del Mal del Pinto en la Republica Mexicana 1939-1931 Dept Salubr Mexico, 1934) 11% of 2,500,000 people have it Fernando (JTropM 37 376, 1934) in Ceylon Saenz et al (ADS 41 463 1940) spirochetes in scrapings, cardiovascular changes in 27%, spinal fluid changes 16%, histologic studies Blanco and Oteiza (Sci 101 309, 1945) transmission to rabbit Perez (abs YBD 194 p. 381), CSF changes in 10 cases like those in syphilis Blanco and de Lacoa (abs YBD 1948 p 360) oral lesions Leon (J 148 932, 1951) in Ecuador yaws only in forest regions, pinta in both rainy and arid areas; yaws in lower levels pinta found higher above sea level, vector of yaws ? Hippelates moseorum. of pinta, the simulium fly main difference is in cutaneous lesions, insidious and benign in pinta, acute and destructive in yaws.

Tropical Blue Disease —A chronic dermatoses occurring in the Chillos Plateau of Colombia affecting especially the uncovered parts of the body and productive of exfoliation and ulcerous mucosal lesions, alopecia, general lymphadenopathy and positive STS was reported by Lecoba (abs J 11 .. 1941) as being due to a spirochete different from *S. pallida* and *S. carate* Whether the distinction from pinta is consequential is dubious.

YAWS

Yaws (Frambesia, Pian) results from infection with *Treponema pertenue* which closely resembles the organism of syphilis. Yaws is endemic in certain tropical countries. The course of the disease may be roughly divided



Figs 459 and 460.—Yaws, the crusted eruption. (Dr J A Johnston, Bureau of Science, Manila.)



Fig. 461—Yaws (Dr Isador Dyer)

Fig 462—Yaws, showing resemblance to syphilitic gummas (Dr J A. Johnston, Bureau of Science, Manila)

into 3 stages a primary stage, including the stage of incubation, which varies in duration from 2 to several weeks or longer followed by the appearance of the mother yaw the analogue of the syphilitic chancre a secondary period marked by the appearance 1 to 3 months after the development of the mother

yaw of a generalized papular eruption which persists for several weeks or months and ultimately a third stage in which gummatous nodules and ulcers occur Reference to primary secondary and tertiary stages in framboesia is inaccurate stated Hasselmann (ADS 66 107 1932) because the primary yaw may last throughout the entire course of the disease and should therefore be called the initial yaw while later lesions might be called generalized metastatic papules, keratodermas or ulcers.

Striking features of yaws (Fox J 123 459 1943) are the normally extragenital manner of inoculation, the keratotic lesions of the soles the absence of mucosal lesions in the early stages, the infrequency with which a secondary eruption is seen, and the clinical identity of late manifestations with those of syphilis.

Some 70% of the cases occur in children under 10 years of age. *T pertenue* infects almost exclusively Negroes in equatorial Africa, in the Pacific islands including the Philippines, Malay States, Burma and Thailand, and also in Haiti, Santo Domingo, Jamaica, and parts of South America. The initial lesion often occurs on the leg, perhaps



Fig. 463.—Yaws corymbose, papulosquamous eruption. (Dr O. G Costa.)
Fig 464—Yaw leukoderma (Dr O. G Costa.)
Fig 465.—Yaw psoriasiform lesions in a pot bellied child (Dr O G. Costa.)

inoculated by flies. The mother yaw when it is seen, clinically resembles the common frambesiform eruption excepting its larger size. The typical secondary eruption, when seen, more resembles impetigo than any manifestation of syphilis. Volar hyperkeratotic lesions of yaws seen often in the West Indies may result in a crablike gait Lesions resembling lichen scrofulosus are sometimes observed. Pigmentary changes like those in pinta are found. While spinal fluid changes were demonstrated in half the cases examined, no symptoms of neurologic involvement were reported by Pardo-Castello (ADS 40 762, 1939) in a valuable study of 500 cases in Cuba. Iritis does not occur Juxta-articular nodes may reach the size of an orange in a decade or more of persistence and slow growth (Chambers ADS 50 105 1944) Osseous involvement is common, with more rapid and painful manifestations than occur in syphilis (Helfet JB&JSurg 26: 672, 1944) Marked x ray changes develop in only a few weeks perhaps simulating osteomyelitis following trauma and accompanied by fever swelling and muscle spasm. Sites of predilection are the tibial, distal femoral, medial clavicular and distal humerus regions. Osseous as well as other manifestations are dramatically responsive to antisyphilitic chemotherapy

Lesions of the aorta and other viscera in yaws can not be distinguished from those of syphilis on histopathologic grounds (Weller AmJSyph 20 467 1936; 21 357 1937)

Gangosa (Rhinopharyngitis mutilans) is the name applicable to ulcerative granulomatous destruction of the palatine, pharyngeal and nasal tissues occurring in yaws as a progressive mutilating manifestation (Stitt USNMB 24 1 8 1926) It was recognized as being due to yaws, not syphilis, by Leys



Fig. 466—Yaws mucosal lesions. (Dr O G Costa.)



Fig. 467—Yaws lesions resembling lichen planus. (Dr O G. Costa.)



Fig. 468—Yaws lesions of mother's breast and infant's face. (Dr G. Henggeler MonatshPraktD 11 336, 1905.)



Fig. 469—Yaws. (Dr A. J Geiger.)

in 1904 and was found responsive to antisyphilitic treatment by Odell in 1910 Cases had become rare by 1916 but old, cured patients could be obtained for exhibition, stated Johnson and Depping (USNMB 10 667 1916) Earliest lesions were superficial ulcers of the pharynx or tonsil and the rate



Fig 470.—Osseous nd periosteal lesions of fingers in late yaws. (Drs. C. L. Pickett nd L. M. Pickett.)
Fig 471 —Y w ulcer of ankle. (Dr S A. Winsor)



Fig. 47_—Gangosa, early stage. (Dr A. J Geigr)



Fig 473.—Gangosa. (Drs Musg e and Marshall)







Fig 474 —Gangosa. (Dr A. J Geiger)
Fig 475.—Gangosa, healed and scarred. (D A. J Geiger)
Fig. 476 —Gangosa, advanced stage. (Dr A. J Geiger)

of destruction might be rapid or slow with little pain and sometimes with periods of quiescence followed by further progress (Mink and McLean J 47 1166 1906 JCutDis 25 503 1907) See Fordyce and Arnold (JCutDis 24 1 1906) Crichlow (JTropM 24 74 1921) Solomon Islands cases; Lahiri (IndianJPed 15 73 1948)

T pertenue the causative organism of yaws, was discovered by Castellani (BMJ 2 1280 1330 1438 1905) It induces the same serologic phenomena as *T pallidum* for STS become positive in yaws as in syphilis. *T pallidum* and *T pertenue* cause different diseases in animals (Turner AmJHyg 25 477 1937; Ferris and Turner APath 26 491 1938) When the attempt was made to inoculate yaws into syphilitics there were no takes (Turner AmJHyg 23 431 1936)

Treatment.—Penicillin is effective (Whitehill and Austrian BullJHH 75: 232 1944) de Cunha et al. (J 126 1163 1944) Hill et al. Lancet 2 522, 1946 Dwindelle et al AmJTropM 26 311 1946 27 633 1947) Relapses occur as in syphilis. Yaws is as hard to cure as syphilis, and it is treated in the same way Yet a single dose of repository penicillin, which may be all that circumstances permit yielded worth while results in epidemiologic work (Arje USNMB 47 966 1947) When penicillin treatment was more ade quate seronegativity was attained in 59% of the cases in one year (Rein et al. ADS 57 942 1948 JID 14 239 1950)



Fig. 477—Circinate lesions of the face i yaws.

Fig. 478—Same patient as in Fig 477 one week after treatment with 600 000 units of penicillin. (Gradwohl et al Clinical Tropical Medicine, Mosby 1951)

Aureomycin by mouth constitutes effective treatment (Ampofo and Findlay TransRoySocTropM&H 44 311 1950) and so does Chloromycetin (Id. ib p 315) Terramycin, too will eliminate spirochetes in 24 to 48 hours and produce striking healing of ulcerated lesions, and seemed better than penicillin to Loughlin and Joseph (abs YBD 1951 p 93)

See Pearce and Brown (JExperM 41 673, 1925) orchitis in rabbit, Fox (ADS 20 820 1929) differences from syphilis; Butler (ADS 32; 440, 1935) epidemiology Kitamura (DZtschr 71; 61 1935) morphologic identity of T pallid m nd T pertenue Butler (Syphilis et Morbus Humanus, Science Printing Co, 1936) identity of yaw and syphilis Hoffmann (ProcfrancD 43 1200 1936) differences de Wytt (JRoyArmyMC 81 256, 1943) in West Africa troops; Friedheim (AmJTropM 29 185, 1949) treatment with STB orally deri ati of acetarsone; Jelliffe (JTropM 53 228, 1950) "ghoul hand"; Hackett (Bone Lesions of Yaws in Uganda, Oxford, 1952) 242 cases, osseous lesions Hill (Atlas of Framboesia, World Health Organization, see BJD 64 34, 1952); Guimaraes (abs AmJSyph 37 593 1953) Brazilian data Hackett (BMJ 1 74 1953) World Health Organization principles and practice of control First International Symposium on Yaw Control (W H O monograph, Geneva, 1953, bs AmJSyph 38 77 1954)

BEJEL

Syphilis mo g th Bedouins i called bejel. Hudson (ADS 33: 994, 1936; AmJSyph 21: 45 1937; BJVD 27 174, 1931) described this interesting community i fection, which among the isolated peoples f th Middle Euphrates Valley is contracted nonvenereally in ch ldhood n the majority of instances. The epidemiology of bejel is comparable with that f yaws. The esponse to bismuth therapy is favorable. This mild type of spirochetosis is thought to be due to a mild strain of the organism. The public health and economic spects of it were studied by Hudso and Crealey (JTropM Sept. 2, 1936, p. 246) According to Hasselmann (ADS 38 837 1938) the exclusive transmission of syphilis

among Arabs by nonsexual means is a myth. Hasselmann considered *bejel* simply one of many colloquial names for syphilis, all these names being indiscriminately used for all cutaneous ulcers. Syphilitic abortion is commonplace. The disease is not yaws. It is misleading and confusing to call [syphilis] by different local, colloquial names for it runs the same course [among the Arabs] as elsewhere. Syphilis, yaws, pinta, and bejel were interpreted as various modifications, mainly on climatologic grounds, of one disease by Hudson (*Treponematosis*, Oxford Univ Press, 1946). Cases affecting the central nervous system have been observed (Akrawi BJVD 25 115, 1949) and 3 cases of uncomplicated aortitis were described by Akrawi and Rahim (*BJVD* 27 95 1951).

See Rost (ADS 40 305, 1939), bejel *is not* syphilis. Hasselmann (ADS 40 304, 1939), bejel is syphilis. Wilcox (Lancet 1 556, 1951) Southern Rhodesia "njovera," an endemic disease usually contracted in childhood, indistinguishable from syphilis, probably same as bejel. Rink (AmJSyph 35 291 307 1951) rabbit infections do not distinguish syphilis, yaws and bejel. Marshall (BMJ 1 1331 1951) racial variation in syphilis, hypopigmentation in black skin, witkop in South African natives. Csonka (BritJVD 29 95, 1953) 3,607 cases in Iraq, WHO campaign, penicillin cures. McFadzean and McCourt (BMJ 2 1270, 1954) treponematoses in Gambia resembling bejel, drinking cup transmission in small children.

SYPHILIS

Syphilis is an infectious disease due to *Spirochaeta pallida* (*Treponema pallidum*) of great chronicity, systemic from the outset, capable of involving practically every structure in the body in its course and of simulating a large proportion of the entities comprising the field of medicine and the specialties, distinguished by florid manifestations on the one hand and years of asymptomatic latency on the other, transmissible to offspring in man, transmissible to certain laboratory animals, and specifically treatable to the point of presumptive—but not thus far demonstrable—cure by the use of penicillin, derivatives of arsenic, mercury and bismuth and fever therapy (Stokes et al. Modern Clinical Syphilology, Saunders, 1944). Since the time when Stokes et al. expressed doubt about curability with penicillin, this doubt has been dispelled.

Syphilis is widespread among the populations of every country. In the United States of America it was generously estimated that 500 000 new infections were contracted during 1935 and that the cost to the nation annually approximated half a billion dollars. The incidence in 2 million draftees approximated 4% in the white and 20% in the Negro (Vonderlehr and Usilton J 120 1369 1942). It is likely to cost taxpayers a great deal more (Stokes et al. AmJMSc 109 586 1940) although there is no doubt of the profound diminution in the number of cases seen by most practitioners since 1950.

General References v Baerensprung (Die Hereditäre Syphilis), Hirschwald, Berlin, 1864. Fournier (Syphilis and Marriage), Morrow translation, Appleton, 1882. Bulkley (Syphilis in the Innocent) Bailey and Fairchild, 1894; Finger (Syphilis u. Syphilisähnliche Erkrankungen d. Mundes), Urban & Schwartzenberg, 19 2. Handbuch d. Haut- u. Geschlechtskrankheiten, edit. by Jadassohn, Springer 1927-1931, vols 15-19. Noguchi (Laboratory Diagnosis of Syphilis) Hoeber, 1923. Parran (Shadow on the Land) N Y 1937. Eagle (Laboratory Diagnosis of Syphilis) Mosby 1937. Dennie and Pakula (Congenital Syphilis) Lea & Febiger 1940. Moore (Modern Treatment of Syphilis) Thomas, 1941. Hazen (Syphilis in the Negro) VDI Suppl. #15 1942. Kampmeier (Essentials of Syphilology) Lippincott, 1943. Stokes et al. (Modern Clinical Syphilology) Saunders 1944. Dattner (Management of Neurosyphilis), Grune & Stratton, 1944. Moore (Penicillin in Syphilis) Thomas, 1946. Wile (Proc Inst Med Chicago, 16 340 1948) unsolved problems in syphilology. Beerman (JID 9 113, 1947) problems and research opportunities. Rosahn (Autopsy Studies in Syphilis) JVDI Suppl. #21 1947.

Historical References Pusey (History and Epidemiology of Syphilis), Thomas, 1933. Rosenthal (ADS 40 39 1939) old epidemics. Kemp (AmJSyph 24 739, 1940) interesting outline and bibliography. Holcomb (BullHistM 10 148, 1941) stimulating Columbus. Goodman (Notable Contributors to the Knowledge of Syphilis) Froben Press, 1943. Moore (AmJSyph 29 133, 1945) history of treatment. Truffi (I'CutR 81 515 1947), Hieronymus Fracastor. Cole (ADS 64 13 1951) Moore (AmJSyph 38 487 Nov. 1954), obituary of AmJSyph, last issue. Cole et al. (AD 71 231 1955) pre-Columbian skeleton from Arizona showing syphilitic changes.

Review of Literature Moore (AIntM 54 1076, 1935). Padget and Moore (AIntM 58 901 1936, 60 887 1937). Padget et al. (AIntM 62 1029 1938). Moore and Mohr (AIntM 64 1053, 1939). Mohr et al. (AIntM 66 1112, 1940 69 478, 1942). Clark et al (AIntM 74 390, 1944).

Acquired Syphilis

Course and Pathologic Background of Untreated Syphilis (after Stokes et al. 1944).—A primary incubation period follows inoculation. Although there are no clinical signs of infection during this time, reproduction of spirochetes progresses rapidly in perivascular tissues with general hematogenous dissemination in a very short time. The primary stage is marked by the appear-

ance of the chancre with wide variability in the local reaction. There is satellite lymphadenitis, and systemic symptoms may be manifest such as headache, bone pains, lassitude and malaise. The chancre is produced by lymphocytic and plasma cell infiltration to form a papule at the site of inoculation. Reproduction of *organisms here is at its height* *Other foci of similar inflammatory* structure are developing throughout the body their number location, and activity dependent on the virulence of the organism and the peculiarities of the host Spirochetal septicemia is present. Serologic alterations begin which result in specifically positive reactivity to tests.

The chancre begins to heal in the early secondary stage and disseminated manifestations develop with lymphadenitis, skin lesions, enlargement of the spleen, and osseous, cerebrospinal, hepatic and nephritic lesions. Serologic reaction is now positive. Local immune reactions begin to destroy spirochetes in the chancre and elsewhere and healing sets in. Enormous numbers of new foci are established in the skin, bones, lymphatics and viscera. Lymphocytes *disappear from the healing foci and fibrosis occurs. The organisms are partially destroyed or suppressed.* Activity declines throughout most of the body but innumerable foci remain in the perivascular lymphatics and lymph nodes.

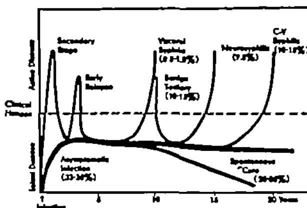


Fig. 473.—The possible courses of syphilitic infection, diagrammatic. (Morgan: J 112 311 1939)

Late in the secondary stage the eruption tends to disappear spontaneously and systemic manifestations subside *coincidentally with widespread destruction of spirochetes.* A few remain and provide the basis for relapse The blood stream contains few of them

With defects of local resistance and revival of foci, occasional showers of spirochetes and crops of lesions may reappear especially on mucous surfaces. The primary lesion and secondary eruption may recur if they had been temporarily aborted by inadequate treatment.

Latency may be established after a time in the prolonged absence of symptoms, or relative quiescence may be punctuated by occasional relapses. Spirochetes are few in number and are held in suppression by systemic and local defense mechanisms. Local lesions, especially of the mucosae bones and skin, may flare. *Chronic inflammatory defense is active but inconspicuous.* It results in degenerative changes and fibrosis. The fetus of a syphilitic woman is likely to be infected.

Latency may persist for many years, but a late phase is likely to appear Its characteristic lesion is the gumma. Gummas are tumorlike masses of granulomatous structure which appear in various organs, skin, liver bones and brain. Endarteritis produces ischemia and necrosis, sloughing destruction and scarring These lesions are comparatively noninfectious, and are apparently due to massive tissue reaction (allergic?) to a small number of organisms.

Degenerative lesions of the cardiovascular and nervous systems and fibrosis of parenchymatous organs, such as liver spleen and pancreas, occur in late stages. Spirochetes are present and may be numerous but are usually demonstrable only on special search in microscopic foci in the aorta heart muscle meninges and viscera. Serologic reaction may have become negative.

Infection may be acquired by direct or indirect inoculation, or through the placenta *Infection usually occurs as a result of direct inoculation generally during coitus.* Extragenital infection is common (Rowntree and Hendon J 115 117, 1940) Occasionally one infected person may unknowingly or carelessly infect several innocent individuals (Zimmermann AmJS 23 104 1939) *Moist lesions of all kinds in syphilis are especially dangerous*, a fact which must be made known to every syphilitic and his contacts. The organisms are most numerous in the primary and secondary stages of the disease.

Lesions of the secondary eruption are fairly readily demonstrated to be dark field positive (Agee NOrlMSJ 95 329 1943) An incidence of about 35% of infection of marital partners was noted by O'Leary (PSMMC 15 1 1940) in a study of the spouses of patients whose treatment had been thought adequate as well as of those whose treatment was inadequate The fresher the syphilis of the partner the greater the liability to infection of the spouse, but even 5 years was not enough to render this liability a small one although 10 years sufficed. The blood and lymph are infectious, but the physiologic secretions are not according to Pariser (JID 3 375 1940) Menstrual blood is infectious, and the vagina is therefore periodically hazardous (Pariser AmJSyph 25 339, 1941) Sores in the mouth make saliva infectious (Barnett and Kulchar JID 2 327 1939) The spinal fluids from 46 patients with secondary syphilis were inoculated into rabbits and in 9 instances infected the experimental animals (Frazier and Pian AmJM 6 443 1949) See Kemp (AmJSyph 22 401 1938) on spirochetes in body fluids.

Spirochete counts in fluid obtained from moist lesions of early syphilis showed 3 700 to 246 000 spirochetes per cmm. while dry lesions yielded roughly one-tenth of this number (Vryonis and Morgan VDI 20 343 1939) Inoculations of from 1 to 6 organisms into rabbits by means of the Chambers micromanipulator failed to transmit the disease (Thomas and Morgan JExperM 59 297 1934)

Infectiousness of untreated syphilis gradually diminishes or immunity increases, until after 4 or 5 years there is considerably less danger of direct transmission inoculation from gummas has been noted, however

A filter passing dark field negative inoculum successfully infected rabbits with the Nichols strain of *S pallida* in the experiments of Wile (AmJSyph 31 109 493 1947)

The Chancre, the primary lesion of acquired syphilis, develops at the point of inoculation usually within 2 to 6 weeks. It generally is a small firm, inflammatory infiltration which becomes eroded and from which oozes a stringy nonpurulent exudate. Spirochetes can be found on dark field examination of the exudate Extragenital chancres are more ulcerative than the usual ones at the coronal sulcus (Wile and Holman AmJSyph 25 58 1941) Most chancres are single but they may be multiple. A chancre may be mixed with chancroidal infection. The lesion may occur anywhere Sites of predilection are glans corona, and shaft of penis, and external uterine os in the female. Primary infection of the distal portion of the penis is unusual in the circumcised male (Hand and Nelson ADS 63 504 1951)

The intraurethral location is not exceptional, induration being palpable as a rule if it is sought, the diagnosis confirmed by dark field examination of material aspirated from the satellite inguinal nodes (Loveman and Morrow AmJSyph 28 79 1944) Frequent extragenital sites are lips, mouth, and hands, especially of physicians and nurses (Downing ADS 39 150 1939) I have seen a woman with chancres on both nipples. Extragenital chancres are often unrecognized, yet Any indolent, indurated lesion anywhere *on the*





Fig. 480.—Syphilitic chancre seronegati primary

Fig. 481.—Chancre of cervix, the common but obscure primary sore in the female. (Drs. Stookey nd Scarpellino.)





Fig. 482.—Chancre of penis. (Drs. J. A. Fordyce and G. M. MacKee.)

Fig. 483.—Multiple syphilitic primary sores, dark field positi in each lesion; coincidental gonorrhea. (Drs. P. B. Stookey nd L. Scarpellino.)



Fig. 484.—Chancre t nus. (Dr. O. L. Castle.)

body especially if accompanied by unilateral adenopathy should arouse suspicion of syphilis (Tucker et al AmJSyph 32 345 1948) and can generally be identified by dark field examination.

The tonsillar primary sore is accompanied by cervical adenitis capable of being mistaken for Hodgkin s disease (Clodfelter ADS 33 535 1936)







Fig. 485 —Chancre of finger (Tucker et al AmJSyph. 32 345, 1948.)
Fig. 486 —Chancre of nail fold (Dr H. F Michelson.)
Fig. 487 —Chancre of finger (Dr J Lamar Callowav)





Fig 488 —Chancre of lip.
Fig 489 —Chancre of foot in first interspace. (Tucker et al AmJSyph 32 345, 1948.)

When gonorrhea and syphilis are concurrently acquired the former may mask the latter particularly when penicillin is used, so that syphilis is partially aborted only to appear later the gonorrheal patient treated with penicillin must be followed for several months (Leifer and Martin J 130 202, 1946)





Fig. 490.—Chancre of eyelid, inoculated by tongue. (Dr Philip Shaffner)
Fig. 491.—Chancre of tongue. (Dr Grover W Wende.)

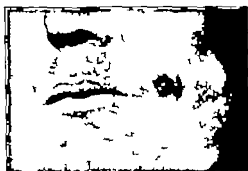




Fig. 492.—Chancre of cheek, following a bite. (Dr Ott Leslie Castle)
Fig. 493.—Chancre of cheek, following a bite. (Drs. O. L. Castle and F J Hall.)





Fig. 494.—Chancre of forehead. (Dr F Roncheese.)
Fig. 495.—Giant chancre of cheek. (Dr Philip Shaffner)

Acquired syphilis is not limited in its incidence to adolescents and adults chancre of the umbilicus of the newborn has been observed and children have been infected innocently (Creswell et al. AmJDisChild 66 611 1943) See acquired syphilis in infants (p 458)

Diagnosis of the Chancre.—Clinical characters are not pathognomonic, and only positive dark field examination is reliable The relatively indolent nature of the syphilitic lesion the long period of incubation, the induration and the lack of response to local medication are typical features. One should select for dark field study lesions which are as young as possible as nearly untreated as possible and as clean and free from detritus and secondary infection as possible (Cares JLCM 29 82, 1944) The chancre rarely may persist for a long time in spite of treatment. Distinction from other genital lesions requires consideration of herpes, granuloma inguinale lymphopathia venerea, chancroid carcinoma etc. (Wilson SouthMJ 41 412 1948)

See Culpepper and Howles (NOrMASJ 8 618, 1935) clinical features unreliable diagnose with dark field, Shackford (USNMB 35 469 1937) physician chancre Zimmermann (AmJSyph 22 757 1938 23 104, 1939), review bibliography extragenital chancres, Hutton (RockyMtMJ 3 191, 1940) extragenital and innocent infections Saduck and Anderson (AmJMSci 203 397 1942) gingiva Ripa and Bartlett (ADS 56 784, 1947) tragus Schipper (IllMJ 75 457 1939) cervix uteri, Lever (NEngJM 231 227 1944) multiple, giant, extragenital lesions Wilcox (BMJ 1 850 1946) accidental, nonsexual transmission.

Inoculation by Transfusion is readily possible and accounts for an occasional case of syphilis acquired without a primary sore (Eichenlaub and Stolar PaMJ 42 1437 1939) This accident to be avoided with meticulous care happens especially when the donor suffers from a seronegative primary infection (Ronchese NEngJM 220 506 1939) Syphilitic osteomyelitis was present despite negative STS in cases of Mandelbaum and Saperstein (J 106 1061, 1936) and Pian and Frazier (ChinMJ 57 301 1940) Prevention requires, of course adequate serologic testing of the donor (Rein et al J 110 13 1938) and physical examination. See Burke (BMJ 2 247 1939) bibliography Arzt (WienKlinWehn 61 105 1949) reject latent syphilitic donors. It is likely that a large dose of repository penicillin given at the time of transfusion would prevent infection.

Mixed Chancres are lesions infected with both *Spirochaeta pallida* and *H ducreyi*. They are characterized by a markedly inflammatory aspect, a tendency to ulcerate extensively and early chancroidal involvement of associated lymph nodes. Chancroidal symptoms so overshadow syphilitic that diagnosis may be seriously confused even until the appearance of a secondary eruption or a positive serologic reaction.

Mucocutaneous Relapse occurred in 6% of some 6 000 patients of a Cooperative Group survey mainly in early cases and shortly after treatment ended The commonest lesion of infectious relapse is the mucous patch papular lesions, moist or dry are also common (Pariser J 113 1206 1939)

Chancre Redux (Chancre Monorecidive) is a form of relapse characterized by the occurrence of a lesion reduplicating the primary sore

Pseudochancre redux is a late, gummatous, syphilitic inflammation appearing at the site of the chancre but the satellite adenitis and positive dark field of a primary sore are lacking

Reinfection after cure can and often does occur (Cannon AmJSyph 17 459 1933 Schoch and Alexander ib 27 15 1943) Reinfections comprise a high but difficultly determined proportion of what must be reported as relapses in evaluation studies of treatment methods. The criteria for diagnosing reinfection were given by Stokes et al (VDI 12 55 1931) see Kopp and Solomon (AmJSyph 23 54, 1939) Clarke and Glicksberg (OhioSMJ 36 517 1940) Shaffer (VDI 24 113 1943) Herman (J 120 283 1942 cases with 3 primary infections in 10 years) Distinction between treatment failures and reinfection was made by Schamberg and Steiger (JVDI 29 92, 1948)

Second Incubation Period.—Following the appearance of the chancre there is usually a second comparatively quiescent period of several weeks.

Vague joint pains, headache slight fever malaise and loss of weight are usual accompaniments. Such symptoms may be mild or severe and they accompany as well as precede the secondary eruption.

Lymph Node Involvement—The satellite bubo which drains the chancre site and appears early is firm painless, freely movable fusiform, olive-sized and typical. It does not suppurate unless the infection is a mixed one. It may be unilateral or bilateral and it is not necessarily on the same side of the body as the primary sore contralateral adenitis usually means syphilis (Fowler BJD 60 279 1948) It is of especial diagnostic importance in extragenital chancres. Herpes simplex also is associated with a satellite gland, but this is large painful evanescent, and in many cases precedes the herpetic lesion.

Immediately after infection takes place spirochetes begin to multiply and invade surrounding tissues, gaining access to lymphatics and blood stream. They are widely distributed over the body even before the initial lesion can be detected. Regional lymph nodes become palpable early in the course of the disease between the fifth day and the tenth They are smooth, firm, oval pea to nut-sized, elastic subcutaneous masses, which are painless and freely movable never fluctuant or matted together Enlargement of epitrochlear occipital and posterior cervical nodes is of greatest import (Beeson ADS 32 746 1935) Too much diagnostic value should not be placed on the presence of palpable lymph nodes, however (Martin Lancet 1 363 1947) They are palpably enlarged in some 70% of early cases. Lymphadenitis in late syphilis is common though frequently unrecognized and is responsive to appropriate treatment.

Fluid obtained from lymph nodes in early syphilis often contains spirochetes demonstrable by dark field examination (Loveman and Morrow Am JSyph 28 44 1944)

Rare cases of syphilitic lymphadenopathy have been known to resemble giant follicular lymphadenopathy (Evans APath 37 175 1944) Enlarged hilar nodes produced a picture simulating sarcoid or Hodgkin s disease in a woman reported by Hornberger (abs J 145 267 1951)

Syphilids are the cutaneous manifestations of syphilitic infection. The eruptions of acquired syphilis were classified by Fox (JCut Dis 31 224 1913)

Early	Late
Macular	Nodular
Maculopapular	Squamous
Papular	Gummatous
Papulopustular	
Pustular	

Cutaneous manifestations of syphilis show great variability in character and in appearance. Lesions may be sparse or diffuse They are generally multiform discrete and comparatively painless, and are never vesicular Because of their multiformity and range of distribution, the lesions may simulate those of many other dermatoses. Syphilids possess certain peculiarities which when considered collectively usually suffice to render clinical recognition possible. They generally develop slowly and in successive crops, which, owing to the tardy disappearance of the preceding lesions, tend to overlap During the exanthematous stage the distribution of the lesions is more or less symmetric, but later especially in relapsing cases, the eruption is often scanty and may involve only certain small areas, favored sites being the nasolabial folds the palms and the upper margin of the forehead. In late stages, the lesions tend to appear in groups and serpiginous and arcuate forms are common. They are usually reddish brownish red or coppery in color Accompanying symptoms often include lymph node involvement cephalalgia, laryngitis and pharyngitis, and eroded papules or mucous plaques in the mouth and other orifices. In the scalp early syphilis may give rise to patchy moth eaten alopecia. Gummatous lesions of the scalp cause cicatrization and permanent alopecia. The nails may be affected at any stage of the disease The

Fig. 496.—Macular early syphilid (Dr J Lamar Callow y)





Fig. 497.—Secondary syphilis

Fig. 498.—Miliary follicular syphilid. (Dr L. W. Ketron.)

forefinger is a likely extragenital site for the chancre. Late syphilids may occur in the nail bed with deformity of the plate Inflammatory or ulcerative paronychia may result

Macular Syphilid.—This is the earliest of the so-called secondary manifestations. It corresponds to symptomatic roseolas of other infections. The eruption is general and symmetric, and usually appears within 3 to 6 weeks after the chancre. The lesions are fairly uniform discrete, erythematous, oval macules. They range from 0.5 to 2 cm. in diameter The sites of predilection are the abdomen sides of the trunk, arms and palms and soles, although no region is exempt. The roseola may be more readily seen at a distance than when close to the examiner It gives rise to no symptoms. It may disappear spontaneously Occasionally it is followed by slight, temporary pigmenta

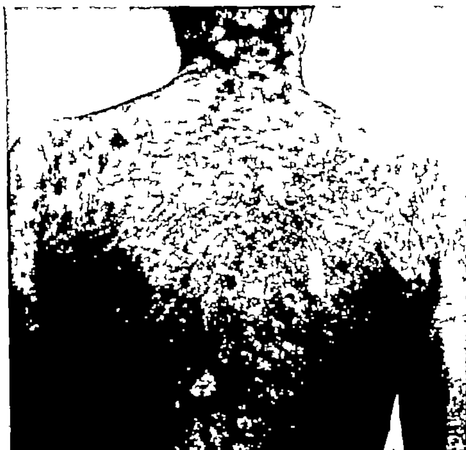


Fig. 193.—Psoriasiform syphilid. (Dr O. G. Costa.)

tion. Recurrences are rarely noted, the lesions being scanty in number segmented or circinate in outline and located usually on the forearms, thighs, and buttocks. If the disease has not been recognized treated, and so caused to recede or if it does not recede because of the autochthonous development of immunity the macules instead of disappearing may undergo further proliferative changes so that macules, maculopapules, papules, and pustules coexist.

Neurosyphilid of Unna.—Persisting roseola-like lesions, sparse nonspreading and capable of progressing 1 to papular lesions or regressing to leave pigmentation, constitute the neurosyphilid of Unna (abs JCutVenDis 8 31 1890; Hall and Schaerrer: ADS 30: 861, 1934)

Vitiligoid and Pigmentary Syphilids.—Melanotic hyperpigmentation of the skin occurs in and near syphilitic lesions, especially when they heal. Vitili-



Fig. 300.—Secondary syphilis, simulating dermatomycosis. (Dr Roy I S Montgomery)



Fig. 301.—Circinate squamous syphilid of arm. (Dr Samuel Sweltzer)



Fig. 302.—"Neurosyphilid" of Ulna. (Dr H H Hazen)

gold depigmentation occurs usually on the back and sides of the neck, consisting of oval ill-defined asymptomatic pigment free patches with hyper pigmented areolae These spots are not pathognomonic. Most of the cases occur in young women. The course is rarely influenced by antisyphilitic treatment (Chargin ADS 2 108 1920)

Papular Syphilid.—For purposes of description, papular syphilids may be subdivided conveniently





Fig. 443 —Papulopustular syphilid. (Dr O L Castle.)
Fig 104 —Pustul syphilid. (Drs. J B. Kessler and J C. Kessler)

Miliary Papular Syphilids are follicular The lesions which are pin point to pinhead size firm acuminate or rounded reddish papules, develop in crops. They tend to be grouped and are generally most abundant on the upper part of the trunk and arms. The eruption is commonly mixed a few lesions presenting summit pustulation and large flat-topped papules commingling with those of the small or large acuminate type In the moist genital and anal regions, the papules tend to be of larger lenticular type and the buccal mucosa is commonly the site of few or many mucous patches.

Lenticular Papular Syphilids may develop closely following the macular eruption, and both types of lesions may be intermixed. The papules are pinhead to bean size or larger brownish or reddish in color with a smooth shining surface which later may become covered with a thin, grayish scale The larger ones are generally flattened and nummular The lesions may be generalized but the sites of predilection are the forehead, face especially the buccal commissures and nasolabial folds, and genitals. They may be discrete or grouped but do not coalesce Pustulation with the formation of papulopustules may supervene



Fig. 505.—Mucous patches. (Dr Sweitzer.)

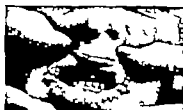


Fig. 506.—Syphilitic split papules. (Dr H. E. Michelson.)



Fig. 507.—Condylomata lata vegetative moist syphilid involving female perineum. (Drs Fordyce and MacKee.)

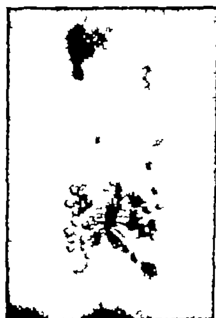




Fig. 508.—Moist papules about the anus.
Fig. 509.—Condyloma latum in left inguinal region, resembling blastomycosis. (Dr Robert N. Andrade.)

PAPULOSQUAMOUS SYPHILID (SQUAMOUS OR PSORIASIFORM SYPHILID).—The lesions are flattish discoid and scaling and may form psoriasiform patches. The papules are dark red and infiltrated with dry grayish adherent scales. The eruption is usually a late or relapsing one of limited distribution. Serpiginous and especially annular configuration is often seen. Concentric and arcuate lesions may develop. The face, scalp, neck, palms and soles in the later stages of the secondary period are the sites of predilection.

MOIST PAPULAR SYPHILID.—As a result of heat and moisture, friction, and maceration, flat papular syphilids in some regions undergo alterations in size and shape. The usual sites for the development of moist papules are the genital, anal and umbilical regions, axillae, buccal commissures, interdigital webs,




FIGS. 310 and 311.—Moist condylomatous and papular vulvar and perianal syphilids, in both cases dark-field positive. (Original of Dr Charles B. Stevenson, from Crossen: Diseases of Women, Mosby ed. 10 1953.)

apposing surfaces of the toes and submammary folds in women. The lesions begin as ordinary flat papules but as a result of their environment become flattened, macerated and covered with a thick mucoid exudate. Ultimately the lesions may become papillomatous. Vegetations occur in the anal and vulvar regions, especially in dirty persons. Purulent matter collects in the interstices of the cauliflowerlike masses, and they stink. Condylomas are moist, flat papules in the anal region which may be mistaken for hemorrhoids, but the general condition of the patient and the presence of syphilitic manifestations elsewhere should serve to prevent error.

PSEUDOSYPHILIS PAPULOSA, described by Lipschütz in 1921, is manifested by an eruption of grouped papules, small in size and asymptomatic, occurring in nonsyphilitic women about the anus and labia, curable by simple cleanliness (Höcker: DWchr 99: 1469, 1934).



Fig. 512.—Annular syphilid. (Dr Lloyd W Ketron.)



Fig 513.—Annular syphilid. (Dr Henry H Hazen.)

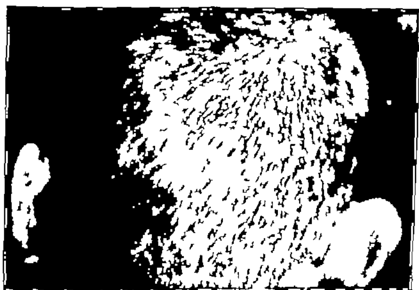


Fig 514—Syphilitic alopecia, showing "moth-eaten" appearance (Drs John A. Fordyce and George M MacKee)

Mucous Patches are flattened, wet abraded syphilitic lesions. They may appear on any mucous surface and are of common occurrence on the oral labial, anal, and vulvar mucosae. The lesions are rounded, flat, grayish superficially ulcerated and teeming with spirochetes. One has a clear grasp of syphilis of the mouth if one bears in mind the fact that lesions there are those which occur on the skin modified only by the influences peculiar to their location.





Fig. 515.—Vitiligoid syphilid.
Fig. 516.—Atrophy and marginal pigmentation of syphilitic scarring.



Fig. 517.—Depigmentation due t maculopapular secondary syphilid in Negro.

Syphilids of the Palms and Soles are usually dry in both the secondary and tertiary stages of the disease Owing to the density of the corneum the appearance of the lesions is considerably modified Macular eruptions of the palms and soles occur as part of the general roseola but papular and nodular forms may be more or less limited to volar regions, especially in relapsing cases. Symptoms are usually absent aside from inflexibility but painful fissures may develop Macerated with sweat, interdigital lesions may simulate dermatophytosis (Dexter ADS 63 581 1951) Wartlike lesions of the volar skin are occasionally seen, constituting the syphilide cornée (Saunders and Youngstrom AmJSyph 34 361 1950) Similarity of the volar lesions of syphilis to those of keratoderma punctatum was interesting in the case of Kerdel-Vegas et al. (BJD 66 449 1954) Compare Pinta, Fig 456 p 375

Atrophy may follow the lesions of secondary syphilis, just as it characterizes the scarring of late lesions. It manifests itself in soft, atrophic macules which may be elevated or depressed, in the distribution of the eruption on which their existence depends (see macular atrophy) Destruction of elastic tissue by the pathologic process is the cause of the lesion. Syphilis is not the only possible cause of macular consecutive atrophy (q v Scull and Nomland ADS 36 809 1937)

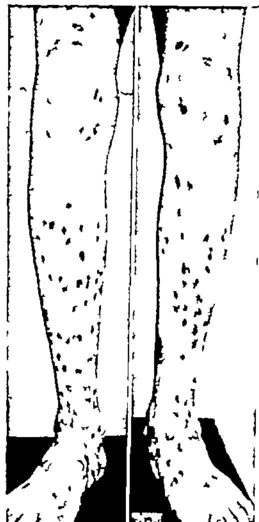


Fig 518.—Secondary syphilis.



Fig. 519 —Secondary syphilis.

Pustular Syphilids may be separated into groups

SMALL ACUMINATE PUSTULAR SYPHILID —The lesions are generally follicular and tiny, and they are likely to be seen along with ordinary acuminate papular syphilids. The pustules are discrete conic, numerous, and symmetrically distributed over the trunk and extremities. They commonly occur during relapses, especially in cases insufficiently treated. On disappearing they generally leave temporary stains and occasionally small scars.

LARGE ACUMINATE PUSTULAR SYPHILID —The lesions, sometimes termed the acneiform syphilid, are pea size or larger discrete, acuminate pustules which are located at the follicular orifices and generally involve the face trunk and limbs. Occasionally the eruption strikingly resembles smallpox and is called a varioliform syphilid The lesions usually develop slowly and in crops. They may be grouped but as a rule they are scantily distributed over the whole body being most profuse on the face

FLAT PUSTULAR SYPHILID.—Lesions of this variety impetiginoid and ecthymiform syphilids, are flat, pea to dime size yellowish or brownish, superficial pustules. On the scalp trunk and extremities, the eruption is usually scattered, but predilection is noted for the face and the genital and anal regions. Large acuminate papules and large flat pustules may be present along with macular elements. The crusts are oval or irregular in outline and of various



Fig. 320.—Squamous syphilid of palm.

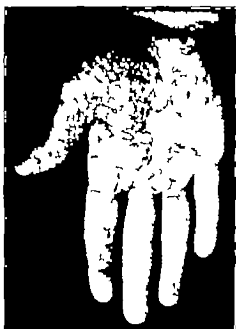


Fig. 321.—Squamous syphilid of palm.





Fig. 322.—Squamous plantar syphilid. (Dr C. C. Dennie.)

Fig 523.—Secondary syphilid. (Dr H. H. Hazen.)
Fig 524 —Malignant syphilis huge ulcerative lesions in early case. (Dr O C Costa)



Fig 525 —Corymbose papulosquamous syphilid of 6 weeks' duration. (Dr J. R. Shelmire.)

thicknesses. Underlying ulcers are superficial and only slightly inflamed or less commonly deep and crateriform with purplish congested areolae Con fluence of lesions may give rise to the formation of extensive crusts. Crusting and ulceration may be conspicuous in early malignant syphilis, constitut ing the rupial syphilid (Thetford and Callaway UCutRev 44 306 1940)

PUSTULO-ULCERATIVE SYPHILID.—The destructive factor is pronounced and the lesions are brownish or purplish in color with infiltrated bases and thick crusts overlying seropurulent exudate, the rupial syphilid.

Diagnostic Features of Secondary Syphilitic Eruptions are

Multiplicity of lesions.
Widespread distribution even if the lesions are few
Discreteness.
Polymorphism: contemporaneous macules papules pustules, ulcers and scales.
Tendency to form circular annular oval, or reniform lesions.
Tendency to group in crescentic, serpiginous or corymbiform arrangements.
Absence of itching, except in follicular eruptions, which itch.
Absence of pain except in digital and infected ulcers.
Involvement of the mucosae, and sore throat.
Generalized lymphadenopathy in which the nodes are painless, small and discrete.
Constitutional manifestations: malaise anorexia, fever headache aching weight loss.
Positive serologic reaction.
Positive dark field.



Fig. 114.—Papulosquamous, lat syphilid of palm.

Seronegativity in secondary syphilis probably does not occur negative reports being representative of diagnostic or laboratory error (Kuhl and Sauer JID 18: 191, 1949)

In primary and secondary cases, spinal fluids showed abnormality in about 5% of the cases (Bauer et al. AmJSyph 36 309 1952) Patients with negative CSF responded to treatment with reversal of STS better than those with abnormal CSF yet, of the latter group, 86% become negative with respect to the CSF on penicillin. When the spinal fluid failed to respond to treatment about half the cases proved stationary while the other half progressed and showed serologic or infectious relapse.

Tuberculoid or Nodular Syphilid occurs late in the course of the disease seldom before the end of the first year and usually in the third or fourth. From both clinical and histologic standpoints, it is gumma of the skin. Lesions range from pinhead to large pea size They are limited in number and are seldom of general distribution. Sites of predilection are the face especially the forehead, scapular and interscapular regions and extremities. Syphilids of this variety exhibit a strong tendency to form groups and to coalesce with the formation of arcuate reniform and serpiginous patches.

Syphilitic tubercles are smooth rounded, circumscribed elevations, reddish or brownish in color and firm in consistency developing slowly and persisting for weeks or months. Tubercles may disappear with or without ulceration, but there is always scarring The cicatrices in the absence of

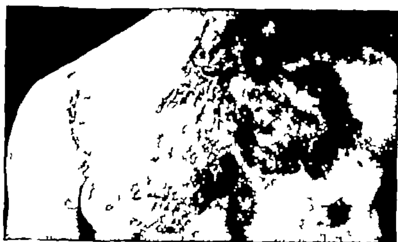


Fig. 527—Serpiginous nodular ulcerative syphilid. (Drs. Kessler and Kessler.)



Fig. 528—Nodular circinate, squamous syphilid. (Dr Grover W Wende.)

ulceration are rounded, atrophic and of mottled hyperpigmentation and depigmentation. In ulcerative cases they are thin glazed and *parchmentlike* occasionally with some scaling New lesions spring up at the borders of the plaques and may undergo regression only to be replaced marginally by fresh ones. So areas of large extent may be affected in the course of years.

Gummatous Syphilid.—In malignant syphilis gummatous lesions may develop early in the disease but as a rule they do not occur before the second year. Gummas are single or multiple, firm rounded, infiltrated granulomas which involve epidermis only secondarily. They are seen as reddish bluish





Fig. 529.—Tubercular syphilid of face. (Dr Harold N Cole.)
Fig. 530.—Tubercular syphilid of nose and cheeks.





Fig. 532.—Circinate squamous syphilid of face.



Fig. 533.—Gummas of scalp and skull. (Dr John W Perkins.)

Fig. 531.—Gummatous and cicatricial late, neglected syphilid, involving face and chest. (Dr Harold N. Cole.)

or brownish pea to walnut size or larger, circumscribed, oval tumors, which may undergo absorption but *generally ulcerate with the formation of soft, sharply defined, punched-out, notably painless sores.* The ulcers are reddish or purplish in color with flabby, necrotic edges and red sometimes greenish, granular floors bathed with mucinous pus. They may involve only the dermis and epidermis, but *subcutaneous tissues are generally attacked.*

The peak incidence of gummatous lesions lies in the first three years following infection, after which there is a sharp drop (Fournier quoted by Wiggall and Hahn AmJSyph 33 270 1949) Yet isolated examples may appear many years, *even as long as 60 years after infection generally being* then associated with neurosyphilis.

Gummas are commonly single but may be multiple The usual sites are the thighs, buttocks, calves, forehead and scalp No region is exempt. *Trauma often determines their location* (Hlgoumenakis abs AmJSyph 24 662 1940) Following an injury to a syphilitic individual, the granuloma may develop instead of physiologic inflammation and healing Diseases as well as injuries serve to localize syphilitic inflammation, and seborrheic dermatitis *may promote the localization of superficial syphilids.*



Fig 534 —Gumma of nose.



Fig 535 —Gumma of buttock.

Ulcerative destruction and *disfigurement are great, especially if the face* is involved An amazingly destructive facial lesion resulting in death was described by Wilhelm and Scholtz (ADS 34 242, 1936) Plastic surgery in the treatment of nasal deformity was discussed by Cinelli (*Laryngoscope* 50 520 1940)

While gummas are here described as they appear in the skin they may affect any organ of the body such as the brain where their presence causes *symptoms of tumor* The location determines the symptoms. In the breast the lesion simulates carcinoma (Braunstein and Woolsey AmJSyph 24 43, 1940) See Osseous syphilis and Visceral syphilis.

See Schmidt et al (AmJSyph 34 182, 1950) penile ulceration, Raich and Nechtow (J 135 347 1947) spinal lesion simulating cancer, Kierland and Underwood (AmJSyph 32 491 1948) gummatous myositis *Laird* (URVD 21 182, 1945) thyroid gland Palmer (AmJSyph 33 481 1949) gumma of stomach.

PRECOCIOUS GUMMA —In malignant precocious syphilis, gummas may develop within a few weeks instead of months or years after infection.

JUXTA-ARTICULAR NODES, or fibroid gummas, are rounded or polylobed firm painless lesions occurring within or beneath the skin in the region of the joints (Greenbaum and Cohane AmJSyph 18 269 1934) They occur in late syphilis in both sexes at any age evolve slowly resemble xanthomas, are associ





Fig. 436.—Gumma of face showing typical "punched out" character

Fig. 437.—Syphilitic interstitial glossitis, smooth atrophy of tongue, leukoplakia, and squamous carcinoma. (Dr George M. Mackee.)





Fig. 438.—Gummatous syphilid, simulating lupus vulgaris. (Dr Gusta Riehl.)

Fig. 439.—Gumma of face. (Dr O. G. Costa.)

ated with positive serologic tests and respond to antisyphilitic therapy Rarely they may soften and ulcerate (Higoumenakis UCutRev 48 223 1944)

See Jeanselme (ParisMed. 1: 242, 1924) Hopkins (BullJHH 49: 5, 1931); McDonald (ADS 43 874 1941); N lan and Jones (SouthMJ 34: 1255 1941); Sweitzer and Winer (ADS 45: 318 1942); Tuta and Combes (ADS 46 375, 1942), Kalz and Newton (ADS 48 627 1943) Kalz (ADS 60: 424, 1949) histology Putkonen et al. (BritJVD 29 71 1953) 4 cases, 3 near trochanters bilaterally cured by penicillin



Fig. 540.—Gumma of nose
Fig. 541—Gumma of wrist.
Fig. 542.—Gumma of popliteal region in a congenitally syphilitic child.



Fig. 543.—Syphilitic gumma of tongue.
Fig 544—Syphil tic glossitis nd leukoplakia. (Dr Clyde L. Cummer)

Witkop (Dikwakwadi, White Head) i a favoid co dition of the scalp, characterized by the formation of white hard, dry superficiall fri b confine t firmly ad herent crusts, wh h give the appearance of a tightly fitting whit kullcap The d sease is chronic and slow evolution. It is see onl am g s philitic ati es f South Africa, being most prevale t in British Bechua aland, where almost the e tire native population is syphilitic.

See Mitchell an l Robertson (SoAfrMJ 13 28, 1915), Fraser (IJD 34 267 1922), MeArthur (AmJSyph 369 1923) M rshall nd Wilson (SoAf MJ 23 783, 1949) syphilis of scalp Marshall (AnndeD 19 33, 1950) scalp cases cured with penicillin, Mapharsen and bismuth.











Fig 545—Serpiginous ulcerative syphilid of the thigh. (Dr F Ronchese)
Fig 546—Serpiginous ulcerative syphilid with scarring of the shoulder region.
Fig. 547—Serpiginous ulcerative syphilid of the back. (Dr Stuart Way)
Fig. 548.—Zosteriform, late syphilid, left dorsal region. (Dr Clyde L. Cummer)
Fig. 549—Gummatous syphilid of thigh and leg. (Dr Royal S. Montgomery)

Deformed Types of Syphilis are those in which inadequate treatment has altered to some extent the expected course of the disease. One must treat seronegative primary cases adequately for with abortive treatment these cases




Figs. 550 and 551.—Facial destruction due to late syphilis in a woman 42 years old. (Dr John W. Perkins.)




Figs. 552 and 553.—Witkop. (Dr Alexander Mitchell, of Pretoria, South Africa.)

relapsed within 90 to 190 days. Early tertiary syphilis after inadequate treatment is likely to result in serious destructive lesions. When gonorrhea and syphilis are both acquired at one time and a small amount of penicillin cures the former then syphilis may appear later with deformed manifestations

(Hailey ADS 50 269 1944) Syphilis so masked may be detected by following the patient with monthly serologic tests for 3 months (Iefer and Martin J 130 202 1946) The lesions of scabies may obscure the diagnosis, its lesions influencing the distribution and appearance of the secondary eruption (Rattner J 131 1241 1946) See Gougerot (J 104 935 1935)

While penicillin given for another diagnosis often confuses the diagnosis of syphilis (Sternberg and LeVan AmPract 3 720 1949) many of the other antibiotics are capable of doing this too

Latent Syphilis.—Patients who have clinically unrecognizable syphilitic infection, with blood serologically positive and spinal fluid normal fall into this class. If no previous treatment has been given or if treatment has been inadequate then adequate treatment should be given Cooperative Clinical Group studies have shown that without treatment the outcome over a period



Fig. 554.—Syphilitic juxta-articular nodes (Kalz and Newton ADS 48 626, 1943.)



Fig. 555.—Bilateral syphilitic bursitus of Verneuil, showing gelatinoid content of ulcerated bursa. A very rare condition. (Dr John D. Lane.)

of years is favorable in 35% but with proper treatment 85% follow a satisfactory course and only 2 to 5% as contrasted with 20 to 30% of the untreated group actually encounter progression.

Progression of the disease in latent syphilis was estimated in a long term study of 926 cases by Diseker et al. (AmJSyph 28 1 1944) Progression was not more frequent among seroresistant patients than among those whose tests reversed in the first year of treatment Benign late syphilids occurred in 2.2% cardiovascular syphilis in 2.2%, and neurosyphilids in 1.5% of the treated cases. The outcome was satisfactory in 94% of the patients. The highest proportion of the progressions occurred among patients who received less than 15 doses of arsenicals. The system of treatment had little effect on the outcome There were 43 deaths in the group and none of these was thought due to syphilis. The optimum treatment reducing the likelihood of

progression to the minimum was about 20 doses of an arsenical and 20 doses of bismuth More than that amount of treatment did not pay off in improvement of the results from the patient's standpoint.

See Stokes et al. (AmJMSc 206 571, 1943) Chargin and Rosenthal (J 107 1274, 1936) fluctuation of serologic tests, O'Leary (NEngJM 221: 764, 1939) criteria of latency; Jordan and Dolce (ADS 34 1 1936) 10-year observations of 189 cases, Harnett et al. (ADS 69 91 1954) progressions despite treatment more frequent among Wassermann-fast cases than among those showing serologic response Chester et al. (AmJSyph 38: 7 1954) patterns of reduction of seropositivity after penicillin treatment.

Osseous Syphilis.—In the secondary stage syphilis commonly gives rise to aching of joints and muscles. Arthritis with limitation of motion but not much swelling or accumulation of fluid, may affect a particular large joint in early syphilis. Periosteal changes usually too slight to show on x ray examination, may appear locally as tender lesions in early syphilis. Verifiable osteitis in early syphilis is similar to that occurring commonly in late benign syphilis (Newman and Saunders NYSJM 38 788 1938 Squires and Weiner ADS 39 830 1939 Reynolds and Wasserman AIntM 69 263 1942) The skull is the usual site especially the frontal, parietal, and nasopalatine bones the sternoclavicular site is next in frequency and the long bones last. Pain and local tumor respond well to specific treatment penicillin being notably effective (Naffziger et al. J 131 1183 1946) Lesions of the skull in secondary syphilis are not rare if they are sought roentgenologically in all cases 7 of 80 secondary cases manifesting them in the experience of Thompson and Preston (AmJSyph 36 332 1952) Head injury apparently determined the site of osteomyelitis of the skull in 2 cases which proved promptly responsive to penicillin (Thompson and Hailey AmJSyph 33: 34 1949) See also Congenital syphilis, osseous (p 460)

Gangrene of a digit without signs of peripheral vascular syphilis was diagnosed by demonstrating spirochetes in the affected vessel tissues by Moynahan (BJVD 24 104, 1948)

See Williams (ADS 33 783, 1936), syphilitic lesions of pre-Columbian bones in North America Epstein (AmJSyph 20 356, 1936), Charcot joints, Stewart (AmJRoentg 40 315, 1938) radiographic changes Halton and Shanks (APath 25 328 1938) stellate scars of Virchow in mound builder skull Weiner (ADS 39, 1006 1939) pathologic fractures Buchman and Lieberman (ADS 44 1, 1941) 119 cases Campbell and Doyl (BMJ 1: 1018, 1954), tabetic Charcot spine, 8 cases Cole et al (AD 71: 231, 1955) pre-Columbian skeletons from Arizona showing syphilitic changes

Cardiovascular Syphilis designates the practical concept of syphilis of the aorta with the cardiac changes secondary thereto (Kampmeier Essentials of Syphilology Lippincott, 1943)

Diffuse myocarditis occurs and is clinically manifested by impaired myocardial function, with palpitation, precordial discomfort, dyspnea on exertion possibly failure. Diagnosis is by exclusion of other possible causes in an inadequately treated syphilitic patient (Mattman and Moore AmJSyph 27: 711, 1943) Gumma may occur in the myocardium, giving evidences of its existence that depend on its location and size.

Aortitis is the common cardiovascular lesion. While invasion of aortic tissues occurs early probably clinical manifestations develop only after some years. The pathologic lesion is the usual perivascular one the vasa vasorum being affected and the wall of the great vessel thereby weakened, scarred and allowed to dilate (Howe AmJSyph 27: 50, 1943) The intima shows longitudinal creases or striation, thickened patches of bluish-gray overlying active disease subsequently to be replaced by depressed scars. The aorta becomes dilated and lengthened, and, since the root of this vessel is the usual site of the process, dilation of the aortic ring occurs with separation of the valve leaflets, and aortic insufficiency as a result. The valves themselves may be involved so that their edges become rolled and thickened. The orifices of the coronary arteries may suffer Thus, by degrees and extent of involvement and by location of the pathologic process, the results of syphilis of the aorta are classed as uncomplicated aortitis, aortic insufficiency and aneurysm.

Necropsy studies of aortas from 45 syphilitics who had and who had not received adequate antisyphilitic treatment showed that few of the former but all of the latter had histologic lesions of active syphilitic aortitis (Webster and Reader AmJSyph 33 19 1949) The aortic lesions in the gross are uneven thin and serpiginous or annuliform, closely resembling the analogous lesions of the skin.

The clinical diagnosis of uncomplicated syphilitic aortitis was discussed by Moore (AmJSyph 33: 43, 1949) Most patients with old syphilis may be assumed to have subclinical aortic disease but opinions conflict regarding what proportion of these develop sufficient clinical evidence to justify the diagnosis. This is based on fluoroscopic demonstration of dilation; increased density and loss of elasticity of the first portion of the aorta lowered cardiac reserve in the absence of hypertension or valvular disease, paroxysmal dyspnea or dyspnea on exertion; localized substernal pain which is typically dull aching relatively inconstant, not influenced by exertion and not referred down the arm; and changes in the second aortic sound, accentuation and alteration described as tympanitic, bell-like or of tambour quality The diagnosis rests on the combined evaluation of relatively insignificant symptoms and signs, and on expert radiologic study Cardiac involvement in congenital syphilis is almost completely nonexistant.

Uncomplicated aortitis was diagnosed in 141 of 547 patients with cardiovascular syphilis by Rich and Webster (AmHJ 43: 321, 1953) The average age was 51 years. Males predominated both in the white and the Negro patients. Of the 141 cases, 15% developed insufficiency or aneurysm within 2.5 years, but their prognosis was no worse than that of the group as a whole and was not affected by the age of the patient at the time the diagnosis of uncomplicated aortitis was made

In aortic insufficiency due to syphilis, the clinical course was divided into 4 phases by Montgomery et al. (AnnIntM 37: 659 195-): (1) the period of aortitis dating from invasion of the aorta until the development of an aortic murmur; (2) the period from the first appearance of aortic diastolic murmur until the appearance of the earliest symptoms of decompensation a period apparently both short and asymptomatic and probably to be estimated as 6 months, more or less; (3) the period from the earliest symptoms of congestive failure until severe congestive failure was present, which in about ¼ of the patients required only some 6 weeks to progress from exertional dyspnea to marked peripheral edema and (4) the period from marked congestive failure to death, which averaged bout 1.5 years. Thus the average length of life after the first appearance of a murmur and the initial manifestations of failure was about 3 years.

Aortitis in more than 1,000 patients followed for 20 years was studied by Webster et al. (AmJSyph 37: 301 1953) Patients free from symptoms at the time diagnosis was made survived considerably longer than patients diagnosed after symptoms had appeared, but of this latter group 29% survived for 10 years or more. Absence of angina and bsence of decompensation were favorable with respect to survival. Some 75% of those who died succumbed to cardiovascular disease The effectiveness of treatment could not be assessed from the data.

The EKG in uncomplicated aortitis or aneurysm shows nothing while aortic regurgitation induces the changes of left ventricular hypertrophy and syphilitic stenosis of the coronary ostia ind ces those of myocardial fibrosis, the ch nges being not of a fixed pattern (Cole and Bohning: AmJMSci 207: 317 1944)

Neurosyphilis was concomitant in some 17% of 123 cases of cardiovascular syphilis studied by Dressle (ConnSMJ 9: 844 1945)

Serologic tests in cardiovascular syphilis were studied by Beckh (AmHJ 25: 207 1943) who found wide discrepancies on this subject in the literature In 100 cases diagnosed at autopsy, STS had been positive in 88% of those with aortic insufficiency and in 86% of those with uncomplicated aortitis. In his cases diagnosed clinically, 96% had positive STS, or had rece ved antisyphilitic therapy or had a clear history of syphilitic infection.

In the treatment of cardiovascular syphilis, it was at one time thought necessary to induce slow rather than abrupt, involution, avoiding Herxheimer reaction and therapeutic paradox. Long preparation with bismuth, mercury and iodides was the practice. Tucker and Farmer (AIntM 80 322, 1947) gave full doses of penicillin at once and did not see severe reactions, the dangers of which they judged had been overrated.

The absence of ill effects of i itial full dosage with penicillin has been ttested by many uthors, luding Flaum and Thomas (AmHJ 38 361, 1949); Bunsek (NYSJM 49: 2176 1949); Edeiken et al. (AmJMSc 217 475, 1949; Circ 1: 1355, 1950, 2: 767 1953); Coale et al. (JK asMS 51: 102 1950); Bruetsch (AmJSyph 35: 253 1951); Wheeler and Curtis (AmJSyph 35: 319 1951); Stokes et al. (J 147 944, 1951); Kampmeier and Morgan (Circ 5 771, 1952)

Penicillin therapy was adjudged harmless by Beerman (AmJMedSci 224: 446 1952) whose review was exhaustive, and its safety was attested also by Edeiken et al. (AmJSyph 37 237, 1953) No harm was observed by Eisenberg and Brandfo brener (AmJSyph 37: 439 442, 1953) in whose 43 cases of uncomplicated aortitis no progression of disease took place afte treatment and in whose 167 cases of insufficiency and 11 cases of saccular aneurysm, 63% noted subjective improvement after penicillin therapy

Untoward effects have been reported (Dolkart and Schwemlein: J 129: 515, 1945) Sudden dilation of an aneurysm followed penicillin and was fatal to the aged Negro patient f Diefenbach (NEngJM 241: 95 1949) A young woman with aortic insufficiency died from the Herxheimer reaction within 24 hours of her first dose of penicillin (Whorton

and Denham: AmJSyph 35: 253 1951) Coronary occlusion was fatal after penicillin was given because of an upper respiratory infection in the case of Butterly and Fishman (J 143 3 0 195_)

Patients who have had previous antisyphilitic therapy may receive penicillin without hazard while the hazard in unprepared patients i so slight it may be stated, a to be disregarded. The dose should be high a total of at least 0 000 000 u. being recommended. Penicillin will take out the spirochetes and the active inflammation but it cannot heal a scar Evaluation of its utility was attempted by Padget et al. (AmJSyph 34: 319 1950) but the data then available we e not decisive. Therapy was judged probably to have improved the prognosis to some extent in any stage of aortic syphilis, definitely more effective if given before the onset of symptoms, then progressively less beneficial by Barnett and Small (AmJSyph 34 301 1950) Histologic studies of patients who received penicillin prior to death showed signs of healing of syphilitic inflammation of the aorta if the antibiotic had been given 10 weeks or longer prior to death (Sinclaire and Webster AmJSyph 38: 54, 1954) Evaluatio of the benefits of therapy is difficult as Johnson et al. (ADS 70 799 1954) pointed out; their patients were only doubtfully better off 5 years after receiving 4,000 000 units of penicillin than if they had been treated with heavy metals and arsenic. They thought 10 000,000 units might have been more advantageous.

The Cooperative Group (Cole et al.: J 108 1961, 1937) reported as follows. *Of the approximately 500,000 syphilitics in the United States who seek treatment for the first time late in the course of their disease about 50 000 have detectable cardio ascular syphilis. Of this type of involvement 7% occurs within 5 years of the initial infection; it is late in onset Best treatment is prophylaxis. The disease must be treated gently to avoid therapeutic paradox. Uncomplicated syphilitic aortitis is present in 49% of patients with latent or late syphilis.* It i 3 times as common in the Negro as in white persons. The Wassermann test is positive in 7?% and the spinal fluid is abnormal in 49% of the cases. Of 933 patients with early syphilis followed 3 to 10 years, 1 6% developed cardiovascular invol ement of 103 followed 10 to ?0 years, 6 7% developed it. In the 3- to 10-year group not one developed cardiovascular disease if he had been adequately and regularly treated in the early stages of the infection. If aortitis is clinically evi ent, treatment improves the outlook, more than doubling the expectancy Start with a course of metal and use small doses. Aortic regurgitation is seen most often afte ?0 to 30 years nd is associated in 6 % with spinal fluid abnormality In it, 69% had had no previous antisyphilitic therapy and in the remainder treatment had been gi en irregularly and late The average length of life if the heart was in failure before treatment began, was 30 months if not a fa l re 47 months. In 74 cases of aneurysm, 80% of those of the saccular t pe occurred in pat ents 15 to 3 years after infection. Wassermann tests we e posit ve in 90% pinal fluid was abnormal in 64% and clinical neuros phili wa associated 31% No treatment had been rece ved by % Symptomatic relief wa obtained through treatment i 44% those inadequately treated l ved on an average 3? month after diagnosis, whi e those adequately treated lived 75 months.

Details of the internal medical aspects of cardiovascular syphil s will be fou d in such texts as Moore s and Stokes's. Cardiovascular syphilis is largely pre entable by adeq ate treatment of ea ly syph lis (Thompson et al. AmHJ 17 _56, 1939) Rupture of the aorta is a l kely and dramatic catastrophe in a syphilitic with aneurysm.

See Dressler and Silverman (AnnIntM 19 224 1943) early recognition Schamberg (AmJSyph 30 88 1946) in young dults Hu et al. (AmJMed 1 301, 1946), demonstration f l ing spirochetes in orta Heador et l (A nIntM 27 584 1947) aortic insufficiency cases followed for 1 6 years, 26 of 27 cases well compensated and able to continue usual pursu t Thorne et al (AmHJ 38 641 1949) calcification i syphilitic aortitis Peabody t l AmJMSci 219 242, 1950) diagnosis Hejtmancik et al (AmJSyph 34 310 1950), yphil tic pulmonary arteritis ccompa ying aortic Yates (Circ 2 388, 1950) 103 abdominal aneurysms, 1 syph l tic, 3 mixed syphilis and rteriosclerosis Nicol (IIJVD 24 109, 1950) re iew and bibliography Fl um and Thomas (JInsu M 6 27 1951) prognosis Smith et al. (AmJSyph 10 37 1951) syphilitic combi ed w th rheumatic cardiovascul disease, Elsenberg (AmJSyph 36 407 1952) stethograms in early diagnosi Hamper and Sindela (J 153 102, 1952) rupture of eurysm int stoma h Dalenda d I riccbio (J 153 542, 1953), perforation f aneurysm of descending orta into esophagus Bahnson (SGO 96 332, 1953) resection of saccul ortic aneurysms feas ble Johnston et al (PrDiMC 29 721, 1953) resection nd graft of saccula e rysms of thoracic orta DeBakey et al (J 157 203, 1955) treatment in 81 cases f neurysms by ortic resection.

Visceral Syphilis.—Practically every organ is subject to syphilitic damage in either the early or late stages of the infection.

The Lung.—H d log m n festat are those merely of bronic pulmon ry i fection resembling t ber ulosi (W lson AnnIntM 25 134 1946) Exten i e lu g in ol em t wa present a man w th me ingovascula neurosyphilis at died b Librach (BJVD 26 1?0 1950) M l r t berculoid syph li wa found n tw patie t wh nder went ecropsy (Gadek Kl nWehs 28 41 1950) Pleurisy with effu i n occurred in a case of ea ly syph li a most unusual manifest tion reported by Calsan (Tubercle 30 ?60 1949) The lung m y be affected i late benign syphilis, roe tgenograms showing localized shadows or a more w desp ead process. Resemblances to cancer resulted in lobectomy in the patient of Bradley (ADS 55: 444, 1945)

Syphilis of the lung recognizable as such is rare, and it responds quite satisfactorily to penicillin (Kulchar and Windholz: AmJSyph 31: 166, 194).

THE STOMACH.—Gummatous involvement is rare and is difficult to distinguish from peptic ulcer but it is responsive to specific treatment although deformity may require surgical intervention. Infiltrative, ulcerous and tumor types are described, and gross deformity may result (Palmer: AmJSyph 33: 451 1949) Diagnosis is suggested by gastrointestinal compl ints in a patient below the cancer age with hypoacidity and positive STS. The characteristic x ray deformity is f nnel-shaped or hourglasslike the pylorus remaining open because of stiffened wall which interfere with or prevent peristalsis (Bell AmJSyph 33: 234 1931) See Udaondo (Les Gastropathies des Syphilitiq es, Masson, 1936, p. 16)

THE LIVER is commonly affected with late benign lesions of the tertiary sort. Hepatic gummas destroy blood vessels and induce fibrosis. Resolution is followed by deep and extensive scarring The dense scars are generally stellate and deforming, and the organ may be subdivided into lobes hepar lobatum Patients may be asymptomatic, or may have an uppe abdominal tumor usually firm, with low fever attributable to necrosis within the gummata or there m y be slight icterus epigastric pain and tenderness, and ascites simulating portal cirrhosis. The live may be smooth because the nodules are within it or it may be nodular with palpable firm tumors. See Hahn (AmJSyph 27: 529 1943)

Reviewing 9 cases of syphilis of the liver proved by autopsy, Shapiro and Weiner (AmJMSci 222: 494, 1951) noted that the gumma i the characteristic late lesion. The liver may be increased in size but is often decreased. In 62% of the cases the liver was of normal size, while 9 livers exceeded 2,800 grams in weight. The location of the lesion depends on chance, but it determines the progres and sequelae. Nea the surface and distant from the hilum, the lesion does little harm, but a sca close to the hilum is l kely to result in portal hypert nsion, ascites and fatal esophageal varices. The age ra ge was from 22 to 90 years, but the peak incidence was in the sixth decade males and females being equally affected. Of the 79 cases 27 died of syphilis and the cause of death in 70 of them was bleeding from esophageal varices. Hepatic syphilis caused death in 13 cases. Syphilitic involvement of other organs was demonstrable in 39% Only 1 patient was febrile The combination of hepar lobatum and nutritional cirrhosis practically assured the development of portal hypertension. Vascular spiders were present in only 4 patients, 3 of whom were alcoholics. J undice was present in 13 cases, in 10 of which the icterus index was below 20

Jaundice duri g antisyphilitic therapy is confusing for arsenical into ication m y induce it, and infectious hepatitis may occur especially if the virus thereof is inoculated in a treatment clinic by a break of aseptic technic (Mitchell CanadMAJ 48 94 1943; Anderson: BJVD 19 58 1943) It pparently i safe to continue bismuth therapy d ring such jaundice (Forbes: BMJ : 83 , 1944) The low incidence of jau dice in unt eated syphilis of the liver points to its arsenical etiology in t eated cases (Wile and Sams AmJMSci 187 297, 1934) The case of acute yellow atrophy i early philis reported by Zellermayo (VDI 1: 205 1940) was appa ntly due to Mapharsen. See Irgang (ADS 36: 635, 1937); Dermatitis medicamentosa, arsenical, jaundice.

Syphilitic h patiti in early yphilis responds sat sfactorily t arsenicals, according to Leonard (AmJMSci 208 461 1944) who reported a death from acut yellow atrophy in a jaundiced gi l with the secondary rash who had a Herxheime reaction followi g the first dose of rsenic, the becam more j ndiced. When late syphili of th liver was symptomatic, excellent improvement followed the use of penicillin in the patients reported by Tucker and Dexter (AIntM 58 312, 1946)

THE KIDNEY.—Early syphilis occasionally induces a nephrosis in which the uri e is grossly abnormal but function tests are not much altered. The abrupt onset of symptoms, progressive weakness, with anemia, severe edema, massive albumin ria, but little malaise, and dramatic response t therapy were noted n cases by Ola kv a d McCormick (JVDI 28 45 1947) Syphilitic nephrosis may occur n congenital syphilis (Scully and Yamashi: AmJDisChild 77: 652, 1949) Early syphil tic nephropathies heal promptly under intensive specific therapy and leave no sequelae (Thomas and Scharr AIntM 75 679 1946; Scott and Cla k AmJS 30 463, 1946)

Prost tic involvement was reviewed by Bini (AitalD 22: 339 1949)

Ocular Syphilis.—The conjunctiva may be the site of the primary sore. Iritis occurs in perhaps 4% of cases of early syphilis chorioretinitis is un common but occurs in the late secondary stage uveitis with secondary keratitis in late acquired syphilis carries a serious prognosis (Woods AmJSyph 27 133 1943)

Changes in the iris were described in detail by Lowry (SoWM 2 14 1941) Syphilis as a cause of blindness showed no decrease in incidence be tween 1939 and 1948 (Freeble and Donohue J 146 1500 1951)

Chemotherapy combined with fever is effective in acute iritis, interstitial keratitis and syphilitic choroiditis, especially the early cases noted Knight and Schachat (AOphth 35 271 1946) See Neurosyphilis, optic atrophy Treatment penicillin Congenital syphilis, interstitial keratitis.

Neurosyphilis.—*The central nervous system is invaded early in the course of the infection.* Abnormal spinal fluids were disclosed by Cooperative Clinical Group investigations (VDI 18 45 1937) in 25% of seronegative primary 30% of seropositive primary and 33% of early secondary cases. Abnormality may not be noted with standard methods of testing for inoculations into rabbits of apparently normal spinal fluid from patients with early syphilis gave positive results in 14% of the fluids tested by Chesney and Kemp (J 83 1725 1924) Despite the high frequency of spinal fluid evidence of neurosyphilis in early cases, clinical neurosyphilitic manifestations develop in a considerably smaller proportion of untreated patients estimated at from 5 to 10% There is no doubt that self healing occurs in many instances. Treatment adequate by prepenicillin standards in early syphilis reduced the probability of clinical neurosyphilis to 1 or 2% (Moore) but inadequate or irregular treatment was followed by higher rates of incidence If the spinal fluid remains normal for 4 years after infection, the development of neurosyphilis is extremely unlikely

The Central Nervous System is derived from mesodermal and ectodermal tissues. When syphilis primarily inflames the mesodermal meninges and blood vessels, it is called meningovascular When it primarily degenerates the parenchymatous ectodermal tissues, it is manifested as paresis if the brain is particularly affected, as tabes dorsalis if the spinal cord especially suffers, or as taboparesis if both are involved. Admixtures of these types of involvement are usual although acute meningovascular syphilis may produce only the central nervous system manifestations of irritation and toxic psychosis, both of which disappear entirely when treatment is successful. Tabes dorsalis may be present though inactive when the spinal fluid is entirely normal. Among untreated syphilitics, about 5% may be expected to develop paresis and 15% meningovascular syphilis (Moore) Persistently positive blood tests were associated in 74% of the instances with spinal fluid abnormality in the Cooperative Clinical Group material. But serofastness was not necessarily an attribute of asymptomatic neurosyphilis for in about one-third of the cases of early asymptomatic neurosyphilis under treatment the blood became negative yet there was a great tendency for these cases to relapse About 20% of late asymptomatic neurosyphilis showed negative blood tests so that the fact which deserves emphasis is that negative blood tests in treated syphilitic patients do not rule out the possible existence of neurosyphilis (Kampmeier)

Diagnosis of Neurosyphilis.—A high proportion of persons suffering with neurosyphilis are unaware that they ever had syphilis and are unaware that there is anything at all the matter with them Of those patients of Scherlis and Caravati (AmJSyph 30 330 1946) who manifested any detectable clinical abnormality and who were therefore classed as cases of symptomatic neurosyphilis, 86% had ocular abnormalities and 95% of these had abnormal pupils. The incidence of ocular abnormalities increased as the duration of syphilitic *infection increased. Competent ocular examination is a necessity in evaluating* a case of neurosyphilis, and includes the estimation of the visual fields, which may be reduced as the first indication of syphilitic damage of cranial nerves (see optic atrophy)

The diagnosis of neurosyphilis rests primarily on spinal fluid examination. The one spinal fluid test, of the several which standardly should be employed which is diagnostic of syphilis is the complement fixation test, precipitation reactions being little used and less reliable

The Complement Fixation Test must be done in several dilutions, standardly 1.0 0.5, 0.25 and 0.1 cc It is an error to omit the 1.0 cc dilution for many cases are found to be positive with 1.0 cc. yet negative in 0.5. It is desirable to titer the test to a negative reaction so that a base line may be attained for comparison with later findings. If positivity is found at 0.1 cc one desires to know the result with 0.05 which is not rarely positive and with 0.025. A change between consecutive spinal fluid examinations of only 1 dilution may not be significant but if positivity is found at 0.1 cc. at one time and later at 0.5 with 0.25 negative improvement may be estimated to have occurred. The reagin in the spinal fluid is generally of lower titer than in the blood (Wiener and Derby: Arch Neurol 39: 909 1939)

Misleadingly positive Wasserman reactions are indeed exceptional, although they have been reported in some cases of tuberculous meningococcic and lymphocytic meningitis (Scott et al.: AmJSyph 28 431 1944)

OTHER SPINAL FLUID TESTS are the cell count with differentiation of the varieties of cell a qualitative test for globulin the total protein in mg./100 cc., and the colloidal gold or mastic test. Interpretation of the significance of spinal fluid findings has been clarified by Dattner and Thomas (AmJS 26: 21 194) and by Dattner (Neurosyphilis, Grune and Stratton 1944)

ACTIVITY OF DISEASE is indicated especially by increased cell count, particularly when a high proportion of the cells are polymorphonuclear leukocytes, and by increased protein. In general the colloidal curve, a set of digits ranging from 0 to 5 and indicative of the intensity with which the colloid is influenced by serial dilutions of the spinal fluid, parallels the globulin content. Results are reported as 0000000000 negative or 5555554 100 (for example) first zone or paretic type implying the presence of much globulin, or 0002332000 (for example), "syphilitic" or "mid zone" suggestive of less intense reaction. Gold curves help in evaluating the fluid, but are the least significant part of the complete report. When under treatment a series of such curves are obtained and the 5's drop out improvement may be interpreted but many conditions other than syphilis such as meningitis, myxedema, and bloody fluid, also give rise to abnormal gold curves (Merritt and Fremont-Smith: Cerebrospinal Fluid, Saunders 1938) The presence of globulin found by the Pandy or Nonne-Apelt test is abnormal, but not diagnostic of syphilis. Total protein ought to be 40 mg. % or less and is often about 20 in normal fluid but is elevated by any kind of meningeal irritation. The cells of the spinal fluid are especially significant, and 0 or 1 or 2 lymphocytes per cubic millimeter are clearly normal, while 10 WBC is certainly not normal. The exact number of cells to be interpreted as normal or abnormal cannot be given but 5 is a commonly quoted dividing figure I have often seen neurosyphilis develop when the spinal fluid shortly after an "adequate" course of Mapharsen and bismuth showed 4 or 5 WBC, and neurosyphilis would probably have been identified by a Wassermann test using 1.0 cc., a procedure always to be requested of the laboratory When the cell count is high and contains numerous polymorphonuclear leukocytes activity is great. Counts of 100, 200 or more WBC are found in untreated meningovascular syphilis. The count drops rapidly under effective treatment. Low counts are usual in parenchymatous syphilis of the nervous system. The last abnormality to disappear when treatment of neurosyphilis is effective is usually the complement fixation test. Some fluids retain Wassermann positivity as a manifestation of neurosyphilitic latency when all other abnormality has dissipated.

Spinal fluid studies are almost sufficient of themselves in judging the requirement for further treatment (Dattner) If the formula becomes favorable, with diminution of complement fixation titer return of cell count and total protein estimations to within normal limits and improvement in the colloidal test, and if the formula remains so without relapsing, further treatment is unnecessary The spinal fluid cannot be induced to become entirely normal in all patients, by any means, although this is sought and prized if attainable (Thomas and Stokes AmJSyph 29 667 1945)

SPINAL FLUID IS TO BE EXAMINED IN EVERY PATIENT WITH SYPHILIS at some time during the course of his disease. The examination is not necessary in patients with fresh primary or secondary syphilis until they have undergone a course of adequate treatment for this suffices to clear the spinal fluid in a high proportion of the early cases associated with abnormal fluids. After the administration of adequate treatment in early syphilis, it is wise to wait a month or two to do the tap so that one can evaluate the spinal fluid formula when it is not being depressed toward normal by intensive therapy In late syphilis not diagnosed until, say 2 years or more have elapsed since inoculation, and in cases in which the date of infection is not known, spinal fluid examination correctly precedes the institution of antisyphilitic treatment as a necessary preliminary evaluation measure This enables the physician to know whether he is dealing with neurosyphilis or latent syphilis, the distinction being important.

It is further essential to know with what type of neurosyphilis the patient is suffering In only half the cases of neurosyphilis which occurred in the Army personnel studied by Scherlis and Caravati (AmJSyph 30 330 1946) was a trustworthy history of the approximate date of infection obtainable.

Spinal fluid examinations at intervals of 6 months are the best guide to the effectiveness of antisyphilitic therapy judged Dattner et al. (AmJSyph 36 179 1952) on the basis of long time observation of hospitalized patients. When the cell count is normal and quantitative values of other tests have shown satisfactory trends toward normal, then further antisyphilitic therapy will not produce added clinical improvement. Relapse of general paresis and other types of neurosyphilis rarely if ever occurs more than 2 years after effective therapy The CSF Wassermann usually becomes negative in 10 years, but positivity sometimes persists even longer

SPINAL PUNCTURE may be represented as a safe office procedure, is extremely simple in expert hands, and does not require that the patient be kept horizontal for more than a few minutes after withdrawing the sample. A mild sedative given beforehand is helpful; the apprehensive patient suffers out of proportion to the amount he is hurt, which should not be much. The patient can usually be induced to submit to puncture if it is pointed out to him that there is no other way of ascertaining the state of his nervous system, which, for all he or a physician can know, is headed for disaster unless the facts are disclosed in this way. The cisterna puncture is recommended by some authorities (Spiegel: AmJSyph 28: 96 1944). Cisternal puncture by causing subarachnoid hemorrhage killed 4 of 45,000 patients subjected to the procedure although it was performed by experts (Cecil and Johnwick: JVDI 32: 86 1951). Complications following lumbar puncture are rare, but instances of allegedly resultant osteomyelitis of lumbar vertebrae were collected by Redo (Surg 33: 690 1953).

When the specimen is in the test tubes, its cell count should be determined at once.

If the spinal fluid is found abnormal, repeated examinations for evaluating the effects of subsequent treatment are necessary. Each 3 months for the first year is not too much to ask of the patient whose feelings must be considered but whose ultimate welfare must not be frittered away because of his reluctance to do what may reasonably be asked of him. If the spinal fluid is negative in a patient who has had syphilis for 4 years, further spinal punctures are not necessary.

When seroresistance or relapse is encountered following adequate treatment of early syphilis, the spinal fluid must be examined, even if a previous spinal fluid examination was reported negative.

ILL EFFECTS OF SPINAL FLUID EXAMINATION are trivial in comparison with the value of information so obtainable. About 20% of those who undergo the procedure suffer more or less consequential postpuncture headache. This can be incapacitating for as long as 3 weeks, is relieved solely by lying down, may come on days after the puncture, starts with stiffness of the neck and occipital aching and may be limited to these mild manifestations, is to some extent preventable by using narrow gauge needles (Dattner) and is probably due to meningeal irritation which is less likely to be annoying to persons whose syphilis has already produced meningeal irritation. There is no relation between the amount of fluid withdrawn and the incidence of postpuncture headache (Belarra and Carter: J 148: 841 1952). Thorazin 25 mg q.i.d. may relieve postpuncture headache; codeine generally makes it worse. See Pickering (Brain 71: 274 1948); Noon (ArIslM 6: 19 1949); Glesne (Anesthesiol 11: 702, 1950).

The Varieties of Neurosyphilis *are classified as asymptomatic, wherein* no clinical indication of neurosyphilis can be detected excepting the presence of abnormal spinal fluid, and symptomatic wherein various abnormalities detectable by clinical examination are present in addition to abnormality of the spinal fluid. The following descriptions of these are condensed from O'Leary, Moore, Solomon, Stokes and Thomas (BullUSAMD Sept., Oct., Nov. 1944) *and have been modified to accord with the views developed since that date* mainly as a result of the advent of penicillin.

Classification of spinal fluids according to the degree of abnormality observed on examination by each of the 5 standard tests

GROUP	CELLS PER CC	COLLOIDAL GOLD	SEROLOGIC REACTION	GLOBULIN	PROTEIN MG. PER CENT
Group I (mild)	[illegible]	0000000000 to 0001110000	Negative with 0.6 cc	Negative or positive	25-40
Group II (moderate)	20-100	0001110000 to 0245542000	Doubtful or positive	Positive	40-100
Group III (severe)	10-100	5555544210	Strongly positive	Positive	75-150

Mild includes fluids in which the number of cells and content of globulin and protein may be increased, the complement fixation reaction is negative in 0.6 cc and the colloidal curve may be indeterminate or positive. If positive the curve is usually of the syphilitic zone type.

Moderate includes fluids in which the cell number 20 or more per cc., the complement fixation reaction is positive or strongly positive, and the colloidal curve is of the tabetic or indeterminate type. The estimate of the globulin is positive and the estimate of protein shows increase to an average of 60 mg. per 100 cc. Fluids falling just short of the requirement of the severe group are also included in this group.

Severe includes those fluids that have the paretic formula, that is marked increase of globulin, content of protein averaging about 100 mg. per 100 cc., a strongly positive complement-fixation reaction (0.2 cc or less) and the type of colloidal curves indicating dementia paralytica. The number of cells is decidedly increased. In addition to small lymphocytes, large lymphocytes and polymorphonuclear leukocytes may be present.

Asymptomatic Neurosyphilis is characterized by abnormal spinal fluid *findings, but there are neither physical signs nor subjective symptoms of in-*vasion or involvement of the central nervous system. When a patient mani-

fests clinical symptoms or signs which denote that the infection has involved the central nervous system a diagnosis of asymptomatic neurosyphilis is no longer tenable Asymptomatic neurosyphilis may be encountered in any phase of syphilis. It is noted most frequently in early syphilis, in which the incidence approximated 30% under older methods of treatment The rate is much lower than this among well treated patients. The rate among those untreated or those who have not had good treatment for acute syphilis gradually decreases until it reaches an average of 15% of patients in whom the infection is of more than 4 years duration

Asymptomatic neurosyphilis is the forerunner of clinical neurosyphilis but it responds satisfactorily to penicillin treatment so that the development of clinical neurosyphilis is prevented The results of repeated examinations of the spinal fluid are the only indicators of the response that the patient is making to treatment They also denote the trend of the disease in the central nervous system revealing the tendency for the fluid to change to the mild or to the severe (paretic) type

The significance of each test employed in the examination of the spinal fluid must be understood in order to interpret the results of each test intelligently in terms of therapeutic effect and prognosis. Among patients who have asymptomatic neurosyphilis, the earlier in the course of treatment the spinal fluid is examined, the easier it will be to interpret the subsequent changes in the various tests thus observing the trend and response of the spinal fluid to treatment. Re-examinations of the spinal fluid must be done at intervals of about 6 months if the significance of the changes in the abnormalities of the spinal fluid is to be interpreted accurately

It is possible to recognize from the spinal fluid findings that different types of neurosyphilis are impending It is not possible to make such deductions from one but rather from successive examinations of the spinal fluid. For example in a case of asymptomatic neurosyphilis, the paretic type of formula may be reported in the spinal fluid at the time of the first examination If 6 months after treatment the paretic features of the fluid persist this finding then assumes significant proportions if this paretic formula remains, it is convincing evidence that the patient has a resistant type of infection and that the treatment given him has been inadequate On the other hand, some patients who have asymptomatic neurosyphilis manifest a paretic trend in the original test of the spinal fluid, but 6 months after treatment no longer have the paretic features in the spinal fluid in these negative results may be obtained after the second period of 6 months after treatment If the trend of change in the fluid is from the group III toward the less severe types of involvement the inference is that the program of treatment is probably adequate. If the fluid relapses toward the severe type after a rest from treatment a change of the therapeutic program should be considered Patients who have severe and persistent abnormalities of the spinal fluid deserve neuropsychiatric examinations at least every 3 months.

Results of treatment are best in the cases of asymptomatic neurosyphilis in which spinal fluid abnormalities are least severe and in which syphilis has been present for 2 years or less. When the disease has been present longer therapy is frequently not capable of reversing the spinal fluid findings to normal. In such cases the early use of fever therapy used to be advised When the group III formulas were encountered fever was advised at once, but these cases too are known to be responsive to penicillin. See Hahn et al. (AmJSyph 30 513 1946) on prognosis in asymptomatic neurosyphilis.

Serologic negativity occurs spontaneously in some cases of asymptomatic neurosyphilis. Although the incidence of these cases is not known, they are encountered often enough to emphasize the fact that the forces of immunity of certain patients are mustered early in the course of the disease without the aid of treatment and overcome the invasion of the nervous system completely The development of an immune response plus penicillin treatment prevents clinical neurosyphilis almost invariably

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"Moderat includes fluids which the cells numbe 20 or more per cc. the complement-fixation reaction is positi or strongly positi e, nd the colloidal curv is of the tabetic or indeterminate type The estimate of the globulin is positi and the estimate of prot in show an increase t an a erage of 60 mg. per 100 cc Fluids falling just short of the req irement of the severe group are also included in this group.

"Severe includes those fl ids th t have the "paretic formula, that is, marked excess of globulin content of protei a eraging bout 100 mg per 100 cc a strongly positive complement fixation reaction (cc or less) and the type of colloidal curves indicative dementia paralytica. The number of cell is decidedly increased in addition t small lymphocytes large lymphocytes nd polymorphonuclear leukocytes may be present.

Asymptomatic Neurosyphilis is characterized by abnormal spinal fluid findings, but there are neither physical signs nor subjective symptoms of invasion or involvement of the central nervous system. When a patient mani

fests clinical symptoms or signs which denote that the infection has involved the central nervous system, a diagnosis of asymptomatic neurosyphilis is no longer tenable. Asymptomatic neurosyphilis may be encountered in any phase of syphilis. It is noted most frequently in early syphilis in which the incidence approximated 30% under older methods of treatment. The rate is much lower than this among well-treated patients. The rate among those untreated or those who have not had good treatment for acute syphilis gradually decreases until it reaches an average of 15% of patients in whom the infection is of more than 4 years duration.

Asymptomatic neurosyphilis is the forerunner of clinical neurosyphilis, but it responds satisfactorily to penicillin treatment so that the development of clinical neurosyphilis is prevented. The results of repeated examinations of the spinal fluid are the only indicators of the response that the patient is making to treatment. They also denote the trend of the disease in the central nervous system, revealing the tendency for the fluid to change to the mild or to the severe (paretic) type.

The significance of each test employed in the examination of the spinal fluid must be understood in order to interpret the results of each test intelligently in terms of therapeutic effect and prognosis. Among patients who have asymptomatic neurosyphilis, the earlier in the course of treatment the spinal fluid is examined, the easier it will be to interpret the subsequent changes in the various tests, thus observing the trend and response of the spinal fluid to treatment. Re-examinations of the spinal fluid must be done at intervals of about 6 months if the significance of the changes in the abnormalities of the spinal fluid is to be interpreted accurately.

It is possible to recognize from the spinal fluid findings that different types of neurosyphilis are impending. It is not possible to make such deductions from one but rather from successive examinations of the spinal fluid. For example, in a case of asymptomatic neurosyphilis, the paretic type of formula may be reported in the spinal fluid at the time of the first examination. If 6 months after treatment the paretic features of the fluid persist, this finding then assumes significant proportions. If this paretic formula remains, it is convincing evidence that the patient has a resistant type of infection and that the treatment given him has been inadequate. On the other hand, some patients who have asymptomatic neurosyphilis manifest a paretic trend in the original test of the spinal fluid, but 6 months after treatment no longer have the paretic features in the spinal fluid. In these, negative results may be obtained after the second period of 6 months after treatment. If the trend of change in the fluid is from the group III toward the less severe types of involvement, the inference is that the program of treatment is probably adequate. If the fluid relapses toward the severe type after a rest from treatment, a change of the therapeutic program should be considered. Patients who have severe and persistent abnormalities of the spinal fluid deserve neuropsychiatric examinations at least every 3 months.

Results of treatment are best in the cases of asymptomatic neurosyphilis in which spinal fluid abnormalities are least severe and in which syphilis has been present for 2 years or less. When the disease has been present longer, therapy is frequently not capable of reversing the spinal fluid findings to normal. In such cases the early use of fever therapy used to be advised. When the group III formulas were encountered, fever was advised at once, but these cases too are known to be responsive to penicillin. See Hahn et al. (Am.J.Syph 30 513 1946) on prognosis in asymptomatic neurosyphilis.

Serologic negativity occurs spontaneously in some cases of asymptomatic neurosyphilis. Although the incidence of these cases is not known, they are encountered often enough to emphasize the fact that the forces of immunity of certain patients are mustered early in the course of the disease without the aid of treatment and overcome the invasion of the nervous system completely. The development of an immune response plus penicillin treatment prevents clinical neurosyphilis almost invariably.

mal or range up to the first zone type reaction. The complement fixation reaction and flocculation tests vary from normal to the most strongly positive. Any combination in the formula of these tests may be found.

Diagnosis depends on an evaluation of the combined clinical and serologic evidence. The prognosis unless tissue destruction from pressure or scarring has occurred before treatment is instituted is good.

Meningovascular Neurosyphilis.—There is involvement of the blood vessels as well as the meninges. Probably one type of involvement does not exist without the other but when there is clinical evidence of vascular disease the term meningovascular neurosyphilis is used, implying that the meninges are inflamed. The spirochete invades the blood vessel wall and creates the proper condition for the formation of vascular thrombosis.

Resulting symptoms depend on the location and size of the vessel thrombosed. Loss of consciousness, attacks of dizziness, and mental confusion occur. The symptoms also include monoplegia hemiplegia aphasia hemianopsia, cerebellar syndromes, and all types of psychotic behavior. Thromboses rarely occur in the first 6 to 12 months of the infection. They occur more frequently in the succeeding 5 to 10 years with greatest frequency 8 to 15 years after the infection. Characteristic pupillary signs may or may not be present. The spinal fluid gives a group III formula in about 50% of the cases whereas in the remaining 50% weaker formulas of any variety are found.

Tabes Dorsalis (Locomotor Ataxia) is a type of neurosyphilis in which the posterior roots and posterior columns of the spinal cord suffer degeneration with frequent involvement of the midbrain and probably of the sympathetic nervous system. The major symptoms are ataxia pain, visceral crises, diplopia, disturbance of bladder and sexual function, and loss of visual acuity. These symptoms may occur separately or in combination.

Ataxia which is due to the diminution of the sense of motion and position sensation is usually first noted as difficulty in walking in the dark and trouble in making sudden changes in direction and in walking in a straight line. There is usually a sensation in the soles as of walking on cotton or on a thick rug.

Pain of an excruciating lancinating type often described as if a hot wire were thrust into the flesh or as a pinching of the skin is characteristic. Each jab of pain is likely to be instantaneous and repeated over and over again at short intervals for hours or days at a time. Frequently the pain is localized in a small area as in the toe the heel, the ankle the calf, the thigh. The pain may jump from one of these areas to another but often remains in the same spot. At first the pains are mild with long intervals between attacks. As time goes on they become more severe longer lasting and more frequently repeated. These pains are often precipitated by cold wet weather during intercurrent infections or on fatigue. There are infinite variations of the pattern. Some patients describe merely attacks of what seems like a feather being drawn across the skin mild neuralgic pains, or sensations like an electric current being applied to the skin. Many patients suffer from hypersensitivity of the skin especially about the trunk so that the pressure of clothes becomes uncomfortable or getting into a bathtub of warm water is almost intolerable. Some have a sense of constriction about the waist.

Visceral crises of the commonest type are related to the upper part of the gastrointestinal tract characterized by attacks of nausea and vomiting with or without severe cramplike pains or with pain alone. Rectal crises are characterized by pain in the region of the anus and rectum with tenesmus. Sometimes diarrhea at other times constipation, is associated. Other crises such as laryngeal spasms occur. Characteristically these crises occur in spells separated by days weeks or months. In a typical gastric crisis vomiting may last for days, leading to marked dehydration. There are many variants of the gastric crisis. Occasionally one encounters a patient who has regular morning vomiting. Others speak of periodic attacks of indigestion. Duodenal ulcers are not infrequent in patients with gastric crises.

Diplopia is a common occurrence in the tabetic, often the first evidence of the disease Ptosis of the eyelid is also frequent. Paralysis of accommoda tion with internal ophthalmoplegia may also occur Diplopia is the result of partial or complete paralysis of the third fourth or sixth cranial nerve most frequently the third The symptom often disappears spontaneously in the first attack but without treatment there is likely to be a recurrence following which a permanent palsy often results.

Bladder and sexual disturbances comprise loss of bladder sensation lead ing to distention, loss of tone and overflow incontinence and loss of libido and potency a frequent and sometimes early symptom Patients often boast of their capacity to hold the urine all day After voiding there is usually considerable residual urine Secondary infection and pyelonephritis are not uncommon.

Loss of visual acuity due to optic atrophy is a characteristic sign of tabetic neurosyphilis leading to loss of eyesight and complete blindness. Generally it begins with night blindness and more or less rapidly proceeds to complete loss of vision. At an early stage it may be quite difficult if not impossible to differentiate optic retrobulbar neuritis due to an inflammatory process and true tabetic optic atrophy When optic atrophy occurs, the other symptoms of tabes are usually minimum

The objective signs of tabetic neurosyphilis include pupillary changes extraocular palsies diminution or absence of the knee jerks and ankle jerks diminution or loss of vibration and position sense of the lower extremities, more marked in the distal portion Romberg s sign ataxia zones of disturbed sensation about the trunk hypalgesia to pressure on the gonads and the tendo achillis; hypesthesia across the nose and dorsa of the feet.

Argyll Robertson pupils small irregular pupils which fail to react to light but which react during accommodation, are found more frequently in tabes than in any other form of neurosyphilis. The typical Argyll Robertson pupil is often a relatively late sign and is preceded by irregularity inequality and poor reaction to light Although the tabetic pupil is often small, in some instances wide pupils may be found and sometimes the pupils respond to neither light nor accommodation See Langworthy and Ortega (Med 22 287 1943) neural lesion Benton (AmJSyph 37 232 1953) description.

Optic atrophy is demonstrated by the pallor of the optic disk, usually associated with loss of visual acuity and with restriction of the visual fields. The recognition of early optic atrophy by ophthalmoscopy and perimetry is possible.

Joint destruction the Charcot joint is a complication resulting from repeated trauma to a joint which has lost some of its normal protective sensi tivity to pain. The Charcot joint often occurs in patients who show normal spinal fluids and evidence of complete arrest of the other tabetic symptoms. Charcot s destruction of an ankle and foot occurred with great rapidity in a patient with poorly controlled diabetes reported by Antes (J 156 602 1954)

Tabes dorsalis can be diagnosed perhaps not until syphilis has existed for 5 years but may develop at any time during the next 25 years. The onset may be insidious, ushered in by flickering pains or by a disturbance in gait or a mild visceral crisis. On the other hand it may occur suddenly One occa sionally meets a patient who collapses and when helped to his feet is markedly ataxic The onset of a severe gastric crisis may be the first recognized symptom. In most cases, however pupillary changes and absence of the tendon reflexes of the lower extremities precede symptoms by many months or years. The course of tabes dorsalis is generally progressive with an increase of symptoms and signs. However some cases undergo spontaneous arrest or develop a negative spinal fluid but this is not necessarily paralleled by disappearance of symptoms.

Spinal fluid findings in tabes dorsalis vary In many during the acute stage of advance one finds a strong formula such as is characteristic of general

paresis. Weaker formulas are found even in the early period of progression and in about 50% of the cases there are moderate pleocytosis, a moderate increase in globulin and total protein, a moderately strong colloidal gold and a moderately strong complement fixation reaction. The spinal fluid may become normal spontaneously

Penicillin therapy arrests the progress of the inflammatory process and the spinal fluid may revert to normal Unfortunately however in many of the cases in which symptoms have existed for some months before treatment is instituted, these persist despite the return of the spinal fluid to normal

See Bennett (J 107 348, 1936) benefit in lightning pains with fever therapy, Rottmann (KlinW hn 16 106, 1937) cobra venom for pains, Simons (AmJSyph 23; 782, 1939) gastric crises, diagnosis and treatment Costello (NYSJM 39 781, 1939) pseudo-Argyll Robertson pupil f Adie' syndrome does not eact to light, but in accommodation its contraction is slow and after accommodation it remains small for 30 seconds It is usually unilateral, usually on the left side and th affected pupil is usually larger and oval Cochems and Kemp (AmJSyph 26 314, 1942) thiamine for lightning pains gave partial relief in half the cases; Brown and Yakorzynsky (ANeurPsych 47 313 1942), vibratory sensibility seems to require both touch and deep-pressure senses Costell (UCutRev 51 280, 1947), Protamide, a denatured proteolytic enzyme from hog stomach, helped half the cases of tabetic pains Koteen (AmJSyph 33 364, 1949) brief symptoms respond better to treatment than those of 2 years or longer duration; if one form f antisyphilitic therapy fails, another is likely to fail, and results with penicillin are only as good as with other methods Dowling et al. (AmJMedSci



Fig 556.—Syphilitic rthropathy "Charcot joints (Dr J P Guequierre.)

217 149, 1949) Myanesin, 1% 1 Gm. maximum dose, I.V relieved pain Rogers (J 140 272, 1949) Priscol stopped pain of tabes and gastric crises QMN (J 140 1312, 1949 143 406, 1950 146 1178, 1951) treatment of pains Kern (J 145 230, 1951) Adi syndrome Fien et al. (AmJSyph 36 201 1952) laryngeal manifestations crises, paralyses, cough, phonia, attacks of suffocation, f tal apneic pasm, rare Koteen and Durnley (AmJSyph 36 231 1952) fever provokes pa n, can be used as provocativ diagnostic test (Grimbl and Csonka (BJVD 28 61, 1952) visceral nalgesia in tabes masking serious internal disease.

General Paresis ((General Paralysis of the Insane, Dementia Paralytica, Psychosis With Syphilitic Meningo-Encephalitis) is a psychosis due to spirochetal invasion of the brain The pathologic changes, consisting of nerve cell atrophy perivascular infiltration, gliosis, and chronic meningitis, exist long prior to the development of mental changes which are the sine qua non of the disease entity

The mental symptoms of general paresis mimic almost any psychiatric symptom complex. The onset of general paresis is usually insidious, although mental symptoms may begin with extreme suddenness. It is usual to obtain a history that before symptoms were recognized there was a period of months during which the patient complained of headache, insomnia capricious appetite loss of weight disturbance of sleep easy fatigability and difficulty in concentration. This galaxy of symptoms is all too frequently diagnosed as

psychoneurosis. In retrospect, it is generally evident that there was a gradual change in the personality and behavior of the individual, with irritability mild memory loss, poor judgment, lack of care in personal appearance, defect in moral and ethical conduct and unexplained deviations in character In other patients the psychosis may be ushered in suddenly by a convulsion or a period of confusion. In many patients one obtains a history that, several years before the psychosis was recognized, an epileptiform or apoplectiform seizure has occurred, perhaps accompanied by hemiplegia or aphasia of short duration.

Classification of several varieties of general paralysis follows the presenting symptoms

(1) A simple dementing form, characterized by loss of memory loss of calculating ability defects in judgment in association with increasing speech difficulty and tremors;
(2) The grandiose form, in which ideas of grandeur and a sense of euphoria are paramount;



Fig. 557—Paresis, with hypomania and delusions of grandeur
Fig. 558—Paresis, with dementia and deterioration.

(3) The manic form, simulating the manic phase of manic-depressive psychosis
(4) The depressed form, similar to the depressive phase of manic-depressive psychosis;
(5) The agitated form, simulating agitated depressions of involutional psychoses;
(6) A schizophrenia like syndrome, with paranoid, catatonic, and schizophrenic features;
(7) Epileptiform manifestations frequently repeated, often characterized as syphilitic epilepsy
The epileptiform seizures occurring in syphilis are of two types grand petit mal attacks associated with dementia paralytica, and so-called syphilitic epilepsy occurring in persons who may or may not show clinical or laboratory evidence of neurosyphilis. Convulsions in paretics are more likely to be relieved by fever therapy than those in syphilitic epilepsy Anticonvulsant drugs are as effective, in any case, as they are in idiopathic epilepsy and should be employed (J 131 873, 1946)
(8) Parkinsonian manifestations, rarely seen as a result of neurosyphilis (Neill: BMJ 2: 320 1953)

The neurologic signs encountered in general paresis are variable. Pupillary changes occur frequently but are often absent in the early stages of the disease Irregularity and inequality of the pupils are the most frequent of these signs found early Disturbance in the light reaction may occur with

the Argyll Robertson pupil or complete fixation ultimately developing Dilated pupils are more frequent than miotic ones. Speech defects or disorders of articulation are probably the most characteristic somatic disturbance of general paresis. A break in the voice tremulousness, overactivity of the facial muscles even including the orbicularis oculi with stumbling over consonants should raise the question of general paresis. In the early stages, the speech defect is demonstrated by having the patient repeat difficult test phrases such as Methodist Episcopal or Third Riding Artillery Brigade but it is often recognizable in spontaneous speech Tremor is a frequent and early sign and is seen in the facial muscles, the protruded tongue and the extended fingers. Rapid alternating movements of the hands and fingers are poorly performed. The tendon reflexes are often exaggerated if tabes is coexistent they are diminished or absent. Persistent signs of focal damage when they occur suggest that the case is not one of pure paresis.

The course of untreated paresis is downhill, leading to extreme mental and physical deterioration and death In untreated cases about one-half die within 30 months of the onset of mental symptoms and almost all are dead within 5 years. During the course of this downhill trend, epileptiform and apoplectiform seizures are frequent. An interesting characteristic of the paretic apoplectiform seizure is the tendency for a quick recovery from the apparent focal brain damage Following each convulsive attack increased mental deterioration may ensue From 10 to 20% of patients have spontaneous remissions lasting for several months to a year followed by relapse

The spinal fluid in general paresis is characteristic The cell count varies from normal to 80 or more per c mm. globulin is present in large amounts, the total protein varies from 75 to 150 mg per cent the colloidal gold test is of the first zone or paretic variety The complement fixation and flocculation tests are strongly positive Little variation from this formula is consistent with the diagnosis of general paresis.

The prognosis of general paresis under treatment is in the majority of cases an arrest with some residual defect the extent depending upon the amount of damage which occurred before treatment became effective. Whether every case in which the physical state of the patient permits should have fever therapy as well as chemotherapy which has been the consensus in the past, is debatable in the light of more recent knowledge of the effectiveness of penicillin therapy The pathologic process was arrested by 6 000 000 units, as a rule after which macroscopic brain changes were minimal and residual microscopic changes appeared to be due to neurone destruction antecedent to therapy in the patients of Gianascol et al. (AmJSyph 38 251 1954) While inflammation disappeared following adequate therapy meningeal fibrosis and marginal gliosis might persist and correlation between clinical course laboratory data and neuropathologic abnormalities was not uniform In some cases deterioration continued despite the achievement of an inactive CSF formula and the explanation of this fact is not at present forthcoming (Kral and Dorken AmJPsychiat 109 684 1953) Such patients differ from cases of senile dementia in retaining a better contact with reality and in suffering less fatigability

See Winkelman (AmJSyph 19 [illegible] 1935 24 [illegible] 1936) parenchymatous and interstitial form of spinal cord syphilis [illegible] (AmJSyph 26 [illegible] 1942) spinal cord syphilis Merritt and Solomon (AnnSurg [illegible] 1943), relation of trauma to CNS syphilis Greenblatt and Levi [illegible] (AmJPsych [illegible] 1944) electroencephalography showed abnormalities especially in the [illegible] and paretic [illegible] least in tabes, almost [illegible] convulsive disorder frequently in optic atrophy Merritt et al (Neurosyphilis, Oxford [illegible] Press 1946) [illegible] and pathologic aspects, neuropsychiatric diagnosis [illegible] AmJSyph [illegible] 1948 review of 183 institutional cases showed clinical failure to respond [illegible] treatment failure Thompson and Preston (AmJSyph [illegible] 1950) gumma of [illegible] Lewis (AmJSyph 34 [illegible] 1950) psychometric recognition of early dementing paresis Sternberg and Zimmerman AmJSyph 34 [illegible] 1950) psychologic processes in asymptomatic neurosyphilis defects of reasoning social comprehension, memory and learning

Optic Atrophy Primary optic atrophy is a form of neurosyphilis often seen in conjunction with tabes dorsalis (q v) Untreated it always becomes bilateral and progresses to permanent complete blindness within 7 years

(Moore et al J 111 385 1938) Treatment that was adequate by arsphenamine standards delayed its development and in some instances arrested its progress, while malaria therapy was judged capable of arresting about 85% of the cases. If given while the disease was unilateral about 70% of the sound eyes remained sound, Moore stated. Good treatment of early syphilis nearly completely protects against its appearance but it occurs in approximately 8% of cases of neurosyphilis (Moore et al. AmJSyph 26 407 1942) Of the 262,000 blind persons in the U.S.A. some 10 to 15% lost their vision because of syphilis, and of these about 90% were blind because of optic atrophy (Klauder JVDI 32 183 1951)

The pathogenesis is unknown but is somehow related to the organic degeneration which produces tabes dorsalis (Moore and Woods AmJSyph 24 59 116 1940) Histologic studies were reviewed by Bruetsch (AOphth 39 80 1948)

The diagnosis rests upon expert ophthalmoscopic examination, revealing pallor of the discs, especially of the temporal aspects, and on the correct, skillful taking of visual fields and interpretation of them. These examinations must not be omitted in the evaluation of any patient whose syphilis is not primary or secondary (Klauder and Meyer AOphth 43 537 1950) Defect of the visual fields precedes loss of central vision and pallor of discs, and the earliest field losses are for red and green (Klauder et al. AmJSyph 32 574 1948)

Blindness due to optic atrophy should be preventable, if early stages were recognized early and if successful treatment methods were utilized, especially the large total dosage of penicillin (Bruetsch Syphilitic Optic Atrophy Thomas 1953) Comparing treatment with penicillin alone and penicillin plus malaria, Kenney and Curtis (AmJSyph 37: 449 1953) concluded that malaria appeared to add little to the results. They confirmed Moore's thesis that patients with visual acuity better than 6/20 when treatment began tended to achieve arrest while those with worse vision tended in spite of treatment to lose progressively what little they had Problematic indeed are the cases that progress despite treatment. Such cases should be identified as early as possible and given maximum treatment in minimum time and cortisone should be used to supplement retreatment with penicillin (Klauder and Gross AmJSyph 38 270 1954)

Etiology of Syphilis.—Syphilis is due to *Spirochaeta pallida* (*Treponema pallidum*) of Schaudinn and Hoffmann (Arbeit. aus d. k. Gesundheitsamte 22: 527 1905)

T pallidum is a delicate cylindrical spiral motile organism from 4 to 14 microns in length. The number of spirals is from 6 to 15 The organism is anaerobic and is pathogenic to rabbits, anthropoid apes, monkeys and other animals as well as man. Its presence in the tissue fluid of the active primary or secondary lesion can usually be demonstrated by means of dark field illumination. Some staining methods may be equally useful (Krajian AmJSyph 23 617 1939) Similarity of *T pallidum*, *T pertenue* of yaws and *T carateum* of pinta is notable Studies of the morphology of the organism in the tissues by Steiner (APath 29 189 1940) are interesting The end knob and flagella were demonstrated by electron micrography by Wile and Kearney (J 12[illegible] 167 1947)

The organism at first penetrates and multiplies in the mucous layer of the epidermis and lymph spaces of the dermis but diffusion of the spirochetes throughout the body is largely by means of the blood stream. Hematogenous dissemination takes place [illegible] within a few minutes after inoculation (Raiziss and Severac ADS 35 1101, 19[illegible]). The organism dies within a few minutes when dried, but it may remain virulent for days in refrigerated tissues (Rosahn AmJHyg 22 233, 1935 Turner and Fleming: JExpM 620 1939)

Inoculations of from 1 to 6 spirochetes into rabbits by Thomas and Morgan (JExpM 60: 297 1934), using single-cell technic, failed to transmit the infection. Success in transmitting infection by testicular inoculation of rabbits with organisms of the Nichols strain was obtained by Magnuson et al. (AmJSyph 32 1, 1948) almost half the [illegible] when only 2 organisms were introduced. Takes were obtained in almost 90% when [illegible]

organisms were inoculated, and in 100% of intradermal inoculations using *00 000 or ganisms. See Morgan and Vryonis (AmJSyph 22: 462, 1938) quantitative inoculation technic.

See Metchnikoff and Roux (BullacadMéd 1905, p 448) transmission t pes Hoffmann (Di Ätiologie der Syphili) Berlin, Springer 1906 Rosenberger (AmJMSc 1[?]1 14[?], 1906), the spirochet probably does use syphilis Dagi (JPharmExpTher 64 164, 1938) effect



Fig 559 —*T pallidum* ×20,000 (T F Anderson a d J Hillier RCA Laboratory Princeton, N J)





Fig 560.—*T pallidum* da k-field illumination (McCarthy Histopathology f Ski Diseases, Mosby)

Fig. 561 —*T pallid m* stained in section from chancre Orga isms are seen in nd bout the w lls f a blood essel Not bsence of lymphocyt s in early lesion (Dr C C Dennie)

of rsenic is l tri Bessemans nd De Moor (AnnInstPasteur 63 571, 1939) in peri-mental mals Manouélia (AnnInstPasteur 64 449 1940) morphology, reproduction, granular forms Kolmer (AmJSyph 26 156, 1942) citrated blood becomes sterile in 72 hours Morton d Anderson (AmJSyph 6 565, 1942) electron micrographs (Hoeft and Rosahn (AmJSyph 32 59 1948) mouse syphilis Rosahn et l (AmJSyph 33 403, 1949) Brewer medium culti tion technic Morton nd Oakay (AmJSyph 34 34 1950) electron micro-graphs of penicilli effects Campbell and Rosahn (Y l JBiolM 22 527 1950) morphology

and staining characters; DeLamater et al. (AmJSyph 34: 122, 515, 1950, 35: 164, 180, 214, 1951; JID 16: 231, 1951) life cycle; Morton et al. (AmJSyph 35: 503, 1951) flagella; Haanes et al. (AmJSyph 36: 38, 1952) no filtrable forms demonstrable; Rose and Morton (AmJSyph 36: 1, 17, 1952) electron micrographs, no proof of life cycle; Coutts and Coutts (AmJSyph 37: 29, 1953) granules, cysts, buds.

Virulence and Immunity.—The virulence of *T. pallidum* in culture is not great. Considerable variations in biologic characters and virulence of strains of spirochetes are recognized. Vaccine does not alter the immunobiologic apparatus sufficiently to engender riddance of spirochetes from the body. Beck (JPathBact 44: 399, 1937) confirmed the failure of many investigations to demonstrate protective antibodies against the spirochete. Immunity is of the tissues, not humoral (Urbach and Beerman, AmJSyph 31: 192, 1947). Acquired immunity, which can develop only slowly, is responsible for clinical latency, but this immunity is not dependable if unaided by modern therapy and it is inadequate to protect against reinfection or superinfection (Kolmer, AmJS 22: 426, 1938). Recurrence following inadequate treatment of early infections may be more severe than the original reaction to the spirochetes.

Syphilis seems to be a milder disease in women than in men. Some experimental evidence indicates that estrogen given to animals ameliorates their infection (Kemp et al., AmJSyph 22: 9, 1938).

The antibody (reagin) in the complement fixation reaction is apparently identical with whatever substance yields the positive flocculation reaction. In the human being it is a product of infection with the spirochete of syphilis, and also it may be produced by the existence of leprosy, malaria, and other infections. Quantitative studies show that the titer of reagin is rapidly reduced by effective antiluetic therapy (Belding, AmJSyph 24: 29, 1940). The syphilitic antigen is associated with gamma globulins, the separation and purification of which have been studied with great care and with hope of distinguishing the substances responsible for true and falsely positive serologic reactions by Neurath et al. (AmJSyph 31: 347ff, 1947). See Rein and Kostant (ADS 60: 217, 1949) nature of antigens and antibodies, review.

Agglutination of *T. pallidum* in syphilitic serums has received intensive study and appears to have been performed successfully by McLeod and Magnuson (PHRpts 68: 747, 1953) who examined the effect of adding fresh steer serum to mixtures of *T. pallidum* and syphilitic serum. Because of its content of conglutinin, the steer serum caused disappearance rather than immobilization of the spirochetes under the conditions of the *T. pallidum* immobilization test and greatly accelerated and enhanced the clumping of the organisms in the agglutination test. The agglutination test performed by this method appeared to compare favorably in both specificity and sensitivity with the *T. pallidum* test. See Diagnostic tests.

Luetin Test.—The intracutaneous test with spirochetal vaccine analogous to the tuberculin test may be dismissed as being of no practical value. However, it is interesting that the luetin test performed within the scar tissue of a healed late syphilid is negative while elsewhere the patient's skin gives a positive reaction, according to Benceny (DWchr 103: 591, 1939). See Noguchi (Laboratory Diagnosis of Syphilis, Hoeber, 1924) luetin colo plates.

Luetin Therapy.—Spirochetal vaccine used in therapy caused considerable reaction in some patients but no useful immunobiologic effects (Neuber, DWchr 9?: 229, 1934). Immunity acquired by experimentally infected rabbits cured with bismuth therapy was challenged by quantitative inoculations at various time intervals after the animals had been cured, and partial protection apparently was acquired, for from 3 to 4 weeks after infection, it required progressively larger inocula to infect them (Magnuson and Rosenau, AmJSyph 32: 418, 1948). See Wile (ADS 57: 815, 1948); Turner et al. (AmJHyg 48: 173, 1948).

Pathology.—The microscopic lesion is characterized by perivascular round-cell infiltration (Warthin, AmJSyph 2: 425, 1918). Small vessels are the ones mainly involved. The infiltrate in the early stage is made up almost entirely of lymphocytes with a sprinkling of plasma cells. Granulomatous endothelial and fibroblastic proliferation occurs later and more or less giant cell formation is evidenced. The infiltrative clumps of round cells with capillaries at their centers, may coalesce and form what appears to be a massive cellular infiltrate. They may cause vascular obstruction and produce necrosis. Nodules are composed of gross masses of infiltration, and ulcers result from inflammatory infarction and necrosis of tissue. Gummas have the

same basic pathology as other syphilitic lesions. A scar results whether absorption occurs or the weakened overlying epidermis sloughs away Spirochetes are few in late syphilitic lesions in contrast with their profusion early in the infection The reliability of Warthin s criteria for the histologic diag nosis of syphilis was impugned by Rosahn and Schaffer (AmJSyph 28 27 142 1944) whose autopsy material was correlated with clinical data and





Fig. 442 —Acute, early syphilitic inflammation. Chancre, border of the lesion, showing characteristic perivascular lymphocytic infiltration. (Drs Fordyce and MacKee, from Hazen Syphilis—Its Diagnosis and Treatment, Mosby)

Fig 443 —The lementary pathologic lesion of syphilis lymphocytic and plasma-cell infiltration forming a collaret bout a small blood essel. (Drs. Fordyce and M cKee, from Hazen Syphilis—Its Diagnosis and Treatment, Mosby)



Fig 444 —Syphilitic inflammation, from nodula syphilid without lceration, showing gia t cells in gra ulation tissue (Drs Fordyce and MacKee from Hazen Syphilis—Its Diagnosis and Treatment, Mosby)

serologic tests, and indicated that Warthin's lesions were related more accurately to the age of the patient than to proved existence of the disease and that syphilis was not very often the cause of shortened life span. See Rosahn (VDI 27: 293 1940) autopsies.

Staining of T pallidum.—See Krajian (ADS 32 784, 1935) Steiner (JLCM 22: 293, 316 1937; 25 204, 1939), in smears and frozen sections Haire (JLCM 23 1216, 1938); Bailey (JLCM 23: 960 1938) on slide, dry exudate in air cover with N/20 HCl for 10 sec wash in running water 5 sec., cover with Gram iodine 5 to 10 sec., wash, cover with anilin gentian violet 5 sec., wash, repeat Gram. Spirochete stains dark, but not permanently; Friedman (J 112: 134, 1939) distinguish mixed gonorrheal and syphilitic infection by centrifugation of pus in fine capillary tube 12 cm. long, filled by capillarity place this in heavier glass tube to centrifuge 1000 r.p.m. for 10 min., so clearing column of serum to examine with dark field without causing spirochetes to settle Dienst (JLCM 23 646, 1938) nigrosin-formol Kerr (AmJClinPath 8 supp. 63, 1938), improved Warthin-Starry method for tissues Krajian (AmJSyph 22 617 1938) tissues Perrin (AmJClinPath 13 28, 1943) formaldfuchsin; Rosahn and Freeman (AmJSyph 30: 244, 1946) modified Fontana, Onoda (JVDI 26 35 1951); Levine (PHRpts 67 284, 1952), Limura (ADS 67 319 1953) Parker '51 blue-black ink mixed with serum, smeared out rapidly as in smearing blood, dried and examined under oil immersion.

Technic of Krajian Stain.—Sol No. 1 Uranium nitrate 1.0 gram formic acid, 85% 1 cc.; glycerin, chemically pure, 5 cc. acetone 10 cc. alcohol, 95% 10 cc. This is stable and keeps for long periods.

Sol. No. 2: 3 drops of saturated alcohol solution of gum mastic mixed with 7 cc. 95% alcohol. This should be prepared fresh each time.

Sol. No. 3: Hydroquinone, 0.31 Gm. sodium sulfite, 0.06 Gm.; solution of formaldehyde, 40% neutral, 2.5 cc.; pyridine, 2.5 cc. saturated solution of gum mastic in 95% alcohol, 2.5 cc. distilled water 10.0 cc. It is important to use fresh developing solution. This keeps for two or three weeks; when the gum mastic separates and settles, a fresh supply should be prepared.

Rub lesion roughly until it bleeds with swab moistened in alcohol After bleeding stops, smear clear serous exudate and dry in air Flood smear 5 minutes with warm No. 1 Wash in distilled water Apply No. 2 for 2 minutes. Wash off and blow breath over surface of smear then rinse in distilled water Set slide on metal stand. Flood with 1% aqueous silver nitrate made fresh from 10% stock solution. Heat over burner until bubbles begin to form, not boiling, and keep warm 2 minutes. Repeat the silvering process. Pour off silver without washing. Apply thin coat of No. 3. Leave under electric light for 2 minutes while warming gently Wash with distilled water dry in filter paper examine under oil immersion lens. For permanent mounts, dehydrate with absolute alcohol, blot, clear in xylene, mount in dammar

Diagnosis.—Emphasis must be placed on the necessity for careful consideration of the entire symptom complex in every suspected case Dependence on the laboratory for diagnostic aid has grown beyond reasonable bounds. Positive or negative serologic reports in the absence of corroborative clinical evidence may be void of practical meaning or even false but persistently positive tests over a period of several months justify the administration of treatment, and repeatedly positive tests with rising titer make the diagnosis reasonably secure It is a diagnosis to be made discretely advisedly and soberly for the consequences to the patient are great A careful case history and a thorough physical examination of the patient are invariable requirements. In early stages spirochetes can usually be found in material from the lesions or satellite nodes. The evolution of the disease occurrence of mucosal lesions involvement of the lymph nodes and features of the eruption should attract attention. During the tertiary period, cutaneous lesions are generally readily recognizable

The diagnosis of syphilis requires quick suspicion but deliberation in conviction (Grindon JAMA 36 65 1939) and careful examination and prolonged follow up (Friedman and Mazer AmJSyph 22 340 1938) Unsuspected syphilis in the aged constitutes a significant problem in geriatrics (Thewlis and Gale Geriat 3 335 1948)

Contact with infectious syphilis is likely to result in transmission of the disease Abortive treatment is justified and effectual, and if 900 000 units of penicillin in oil is given during the incubation stage protection is almost 100% successful (Alexander et al. AmJSyph 33 429 1949) This view now generally accepted, supersedes the older judgment that treatment should be withheld until the diagnosis becomes unmistakable.

The obligation persists to trace contacts and find cases even though the reservoir of infectious syphilis has undergone marked diminution in recent years, and biologic cure with penicillin in early syphilis is practicable in almost all patients (Kampmeier SouthMJ 46 226 1953)

The history of previous treatment and response to it in detail are especially significant in planning treatment. The occurrence of repeated miscarriages without apparent cause is suggestive of syphilis in women.

The spinal fluid must be examined in all but the fresh cases (Shaw ADS 42 456 1940) The fundamental data to be obtained are (1) the cell count and its differential constituents (2) a qualitative test for globulin (3) total protein quantitatively (4) the colloidal gold or mastic test, and (5) the titrated complement fixation test Without spinal fluid study the diagnosis of latency cannot be made The one abnormality diagnostic of syphilis in the spinal fluid is the positive complement fixation test other diseases are capable of altering any or all of the other aspects of the spinal fluid as syphilis does, but *falsely positive specific tests are extremely uncommon.* Base line studies of the nervous system include evaluation of the psyche and tests of the function of cranial nerves, including examination of the visual fields and ocular fundi of the response of the pupils in light and accommodation, of speech of muscle stretch reflexes, particularly at the heels and knees, and of vibratory and pressure sensibility especially of the lower extremities.

The blood pressure should be recorded bilaterally and the state of the heart and aorta requires painstaking clinical and roentgenologic investigation, preferably fluoroscopic

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Serodiagnosis of Syphilis

(Pages 430–437)

By Charles R Rein MD

Serologic Tests for Syphilis depend on the detection of syphilitic antibodies and, desirably the quantitative estimation of them. Reagin is the name applied to the substance that effects specific reactivity in classic complement fixation and flocculation tests for syphilis. It is now known that several antibodies (q v) exist, and that the one demonstrated by the classic tests can be removed from a serum which thereafter still exhibits syphilitic antibody different from reagin and demonstrable by the newer specific tests *employing Treponema pallidum antigens (TPI TPIA TPA and TPCF tests)* see Antibodies in syphilis (p 433)

In serologic diagnosis of syphilis are used flocculation complement fixation, treponema immobilization and agglutination tests of which the first two have long been standard, while the last in 1954 were new and may be expected to be found of especial value in determining which of the serologic reactors are syphilitic and which are biologic false positives. Flocculation tests entail bringing suspected serum and specially prepared antigen together under suitable conditions then flocculation occurs and is visible if the serum is syphilitic

Complement fixation (Wassermann) tests entail two steps (1) suspected serum has its complement inactivated by heating and is mixed with specially prepared antigen then a known quantity of complement is added with the result that complement is used, fixed if the serum is reactive and is not fixed if it is not reactive (2) the fixation or nonfixation of complement is determined by the result of reaction between the serum, as prepared by step (1) and a hemolytic indicator composed of (a) sheep red blood cells and (b) antisheep-cell rabbit serum which has been heated to destroy its complement. If complement was fixed in (1) hemolysis will not occur on the admixture of (2) and the test is read as reactive a result which may mean that syphilis is present or may mean that nonsyphilitic conditions productive of false positive reaction resulted in the fixation or deviation of complement

Tests must be performed skillfully under standard conditions (Parran et al J 100 4[illegible]3 183 see also *Serodiagnosis of Syphilis* (VDI Suppl. 9 1939 Parts I and II), and Manual of Serology of Syphilis (USPHS 1954) A standard test [illegible] continually being sought ([illegible] Am J Clin Path 18 143 1948)

Results of tests must be interpreted skillfully (Harris [illegible] VDI Suppl. 14 1941). Falsely negative and falsely positive reactions sometimes occur (Kahn [illegible] 30: 92, 1939) The [illegible] of [illegible] positive reaction [illegible] proof that syphilitic affection exists or that [illegible] syphilis must be treated. The existence of a negative reaction *is not* proof that syphilis is not present or that treatment is not necessary See Evaluation of serologic test

The problems of interpretation are very real, for most practitioners have seen clinically syphilitic patients whose serologic tests were reported negative and other patients whom they believed nonsyphilitic whose serologic reports were inexplicably positive. Such discrepancies are not amazing however for one knows that there are no *specific* tests for syphilis, with the apparent exception of the treponema immobilization test devised by Nelson et al. (AmJSyph 34: 101 1950) and other tests employing *T. pallidum* antigens.

Exact details of the methods for performing various tests are to be found in laboratory guides and journal articles to which references are given.

Historical Aspects of Serodiagnosis of Syphilis.—Serodiagnosis of syphilis was inaugurated by Wassermann, Neisser and Bruck (DeutschMWchn 32: 745 1906) with their complement fixation test. Soon after Michaelis, using a similar antigen, the saline extract of syphilitic liver outlined a method for producing visible precipitates with syphilitic serum, thus describing the first precipitation reaction. When Wassermann et al. developed the first serologic test for syphilis (1906), they believed their test to be specific because they employed a saline extract of syphilitic liver for the antigen. They thought it adequately sensitive because positive reactions were obtained with the blood of many individuals with active clinical syphilis. It was soon discovered, however that these antigens were nonspecific for alcoholic lipid extracts obtained from normal tissue were more specific and more sensitive than aqueous extract of syphilitic tissues. Antigenic lipids may be obtained from beef, lamb, horse, guinea pig, rabbit, pig, and human tissues, the heart, liver, brain and muscles being particularly rich sources. Even though these lipid extracts are not true antigens in the biologic sense they do react in an extraordinarily specific manner with syphilitic serum. There are numbers of hypotheses regarding the nature of syphilitic reagins and the mechanism whereby nonspecific lipid antigens produce positive serologic reactions for syphilis. As yet, none fits all the facts. When human heart tissue was used as the source of antigen positive complement fixation reactions were found in about 20% of healthy individuals, reported Osler et al. (AmJSyph 28: 534 1934)

Many methods of complement fixation testing have been devised, but it was not until about 1922 that the great possibilities of flocculation technics were demonstrated. Their first chief advantage was their apparent simplicity. Economy in regard to glassware reagents and expenditure of time prompted their use in many laboratories. Various flocculation tests had reached such degrees of sensitivity and specificity that, in 1928, following comparison with various accepted complement fixation tests at the Second Laboratory Conference of the League of Nations (Copenhagen) the better flocculation tests were considered equal to the better Wassermann tests. Similar results were obtained at the Montevideo Conference (1930) where the best of the flocculation tests were demonstrated to be superior in sensitiveness and equal in specificity to the Bordet Wassermann reaction and its modifications. The results of the American Serological Conferences (1935) in which serodiagnostic tests for syphilis used in the United States were evaluated, indicated that efficient complement fixation tests and efficient flocculation tests for blood or spinal fluid specimens are of about equal clinical value.

Additional conferences held in the United States have shown that at least 5 complement fixation and flocculation tests (Eagle Hinton, Kahn Kline and Kolmer) gave satisfactory results when performed by persons other than the originators.

Improvements in Serologic Methods and Materials.—Combined efforts of research minded serologists and clinicians have done much to improve the procedures employed presently in the serodiagnosis of syphilis. Some recent improvements in laboratory technics and materials are described as follows

Serum Preservatives.—In warm climates, clotted blood specimens become hemolyzed and therefore unsatisfactory for testing. Army facilities found it necessary to separate the serums from the clots to eliminate hemolysis. Frequently it was necessary to ship specimens to distant laboratories, and it was difficult or impossible to ensure sterility in the collection and preparation of serum. During the several days required for specimens to reach laboratory they often became bacteriologically contaminated and unsatisfactory for testing. A suitable substance was needed to prevent contamination without interfering with serologic reactions. Merthiolate (sodium ethylmercurithiosalicylate) proved an excellent antibacterial agent for the preservation of both serum and spinal fluid and for several years has been employed by the United States Public Health Service United States Army and other agencies. In the Division of Serology Army Medical School, serum preserved with 0.1 mg of Merthiolate per milliliter have been used routinely with excellent results (Rein and Bossak: AmJSyph 30 ... 1946) Less than 0.1% of over 20,000 merthiolated specimens were unsatisfactory for testing because of bacterial contamination (Rein and Kelcec AmJSyph 38: 508 1954) Sodium azide is also an excellent preservative.

Inactivation of Serum.—It was long believed necessary to heat or inactivate serums prior to using various flocculation tests for syphilis, and it was thought that such inactivation was necessary only to destroy natural complement present in fresh serums when tested with complement fixation procedures. Investigations by Rein and Pillmer not as yet published elsewhere indicated that fresh syphilitic serum contains a thermolabile substance which inhibits or retards the aggregation of lipid antigens in flocculation reactions. Strongly positive serums often give negative reactions when tested in the raw or unheated state. All serums had to be heated before testing with complement-fixation or flocculation procedures (Rein and Hazay: AmJClinPath 10: 225, 1940) Serums

heated for 10 minutes at 56° C., or for 1 minute at 69.5 C., or for 7 seconds at 100 C. in boiling water gave results practically identical with those obtained with serums heated for the routine 30 minutes at 56 C. Unnecessary prolongation of the heating period tended to destroy some of the reagin in the serums. Rapid inactivation of serum is especially valuable in saving time when rapid flocculation tests are used for the detection of syphilis in donors prior to transfusion.

ANTIGENS.—Considerable progress has been made in the improvement of the various lipid antigens. Isolation of cardiolipin from beef heart (Pangborn JBiolChem 143 47 1941; 153: 343, 1944; ProcSocExpB 48: 484 1941) and the development of methods for the purification of lecithin prepared from both heart and egg yolk (Pangborn JBiolChem 137: 545 1941) have been consequential in improving the serodiagnosis of syphilis. The preparation of cardiolipin antigens for use in various complement fixation, macro- and microflocculation tests has been described by Harris and Portnoy (VDI 3: 353 1944) Harris et al. (VDI 27: 169 1946) Kline (AmJClinPath 10: 68 1946) Brown (JBact 47: 581 1944) Maltaner and Maltaner (JImmunol 51: 195 1945) Kahn and McDermott (JLabClinM 33 1220 1938) Kolmer and Lynch (JVDI 29 160 1948) and Mazzini (personal communication) At the Army Medical School, a cardiolipin antigen was successfully adapted for use in a microflocculation slide test for the serodiagnosis of syphilis (Rein and Bossak: AmJSyph 30 40 1946) The sensitivity of this test was higher than with the Kline diagnostic, Mazzini, Kahn, Hinton, Eagle Boerner Jones-Lukens and Kolmer tests. This increased sensitivity was obtained without a y apparent i crease in onspecificity Extraordinary specificity of the cardiolipin antigen in the presence of malarial infection was repeatedly demonstrated (Rein and Kent: J 133 101 1947)

PRESERVATION OF SHEEP BLOOD.—One of the difficulties in the performance of complement fixation tests lies in obtaining satisfactory sheep blood. Laboratories of modest institutions lack facilities for raising sheep and have to obtain their supply from a slaughter house Red blood cell suspensions prepared from such blood often prove unsatisfactory A preservation technic for maintaining prolonged uniformity in the properties of sheep cells would be a great laboratory convenience. Aseptic collection of sheep blood in modified Alsevers solution at ordinary temperatures and subsequent refrigeration do, in fact permit preservation of the blood for several months w thout appreciable hemolysis or change in susceptibility to lysis by guinea pig complement and rabbit amboceptor it was shown by Bukantz et al. (JLabClinM 31: 394, 1946) Preserved sheep cells are commercially available.

SPECTROPHOTOMETRIC STANDARDIZATION.—Accurate standardization of the hemolytic system in complement fixation tests has become of paramount importance in maintaining constant level f sensitivity To this end the spectrophotometer has been adapted by Kent et al. (JImmu l 53: 37 1946) not only f r quantitative titration of complement and amboceptor and for standardization of sheep cell suspension but also for final readings of the tests themselves The use of this instrument ha been adapted also for complement fixation tests fo other diseases such as malaria (Rein et al. AmJHyg 49: 3, 1949) and amebiasis (Kent and Rein Sc 103 598 1946)

AMBOCEPTOR PREPARATION.—The preparat on of antisheep amboceptor with the elimin tion of rabbit shock is dvantageous to laboratories performing complement fixation tests. The chief difficulty in preparing amboceptor has been the heavy loss of rabbits because f hock part cularly following the injection of the second dose f cells Furthermore when whole cells are employed, finished amboceptor may contai relatively large amoun t of agglut nogen o precipitins, rendering it unsat sfactory fo use A method was de eloped for the preparation of antisheep amboceptor utilizing the cell stroma instead of the packed washed cells by Sawyer and Bourke (JLabCl nM 31 714 1946) The strom i p epared by pecifically hemolyzing wa hed beep cells with mboceptor and compleme t Sati fa tory amboceptor has been produced in about 10 d ys, and titers re h gher tha those usually obtai ed by other methods.

COMPLEMENT SUPPLY.—Most small l boratories do not have fa ilities for maintaining a colony f gu ea pigs necessary for the s pply of complement. Dried o lyophilized gu nea pig serum ha been used n various types of complement fixat on test with ex celle t result Dried gui ea p g complement supplied t the Arm Medical School wa required to meet the following specificatio

(1) T t the xact hem l t unit hould be contained i more th n 0.45 ml of l 30 dilution when titrated by the Kolme method.
( ) *Moist re Content* should not exceed 1% by weight.
(3) *Hemoglob n Cont t* should be minimal.
(4) *Sou f Gu ea Pigs* serum should be obtained from ormal healthy guinea pigs never previously used for a y other purpose
(5) *P serv e Flu d* upplied w th the dried product should cont n 0% sodi m eet te nd % bori acid.

Sev ral commerc al concerns do p epare dried gui ea pig compleme t meeti g these requirements and giving satisfact ry results.

SERUM CONTROLS.—A pos t e nd a egat e serum co trol should be ncluded every time serologic xam nat on re made Th h lps t e sure th sensitiv t of th test employed and tend to min mi the occurrence of techn cal rrors. Ma y laboratories unwisely select fo their cont ol a stro gl pos t serum, wh h i unsat f ctory for detecting a decrease or increase in the sen ti ty f a serologic procedure; for f seas

tivity were reduced or increased by as much as 50% a strongly positive serum might still give a four-plus reaction. The use of weakly positive or partially positive serums would more readily detect changes in sensitivity due to technical error or to deterioration of material employed. If strongly positive serums are utilized, they should be subjected to serial dilutions and tests performed on each dilution. A reduction or increase in titer would then indicate a change in sensitivity. Routine utilization of a strongly positive serum (quantitative control) and weakly positive serum (qualitative control) is of utmost importance in controlling the sensitivity levels of serologic procedures.

OTHER IMPROVEMENTS.—There have been many other improvements, such as (1) the use of recalcified plasma instead of serums for serologic testing (Barnard and Helz: JLabClinM 29: 1-87 1944) (2) the use of the 50% hemolytic unit instead of 100% end point of hemolysis in determining the degree of fixation of complement by specific antigen antibody complex (Wadsworth: Standard Method of the Division of Laboratories and Research of the New York State Department of Health Williams & Wilkins, 1939, p. 224); (3) the introduction of wetting agents for the proper washing of serologic glassware, (4) the use of buffered solution in preparing the antigen emulsions, complement and amboceptor dilutions and for diluting strongly positive serum for the various quantitative tests; and (5) the prevention of nonspecific and prezone reactions in the complement fixation test with spinal fluid by the addition of egg albumen or normal serum to the complement.

Antibodies in Syphilis.—On the basis of experiments with pallida Eagle and Hogan (JExperM 71: 215 1940) demonstrated the presence of 2 antibodies in syphilitic serum: an antilipidal antibody and an antitreponemal antibody. When syphilitic serum was adsorbed with an excess of beef heart lipidal antigen all reagin was removed. The reagin free filtrate still gave agglutination and complement fixation reactions with spirochetal suspensions in the same titer as the original serum. When this serum was adsorbed with spirochetal suspensions, its reactivity with lipidal and with spirochetal antigen was removed.

Other studies confirmed the presence of multiple antibodies in syphilitic serum. Working with palligen 3 distinct antibodies in syphilitic serum, (1) antilipidal (2) antitreponemal (thermolabile) and (3) antitreponemal (thermostable) were demonstrated by D'Alessandro (BollIstSieroterMilan 25: 133, 1946). He expressed the beliefs that in early primary syphilis the antitreponemal antibodies manifest themselves before the antilipidal antibodies; in secondary and tertiary syphilis both types run a parallel course and in cases of prenatal syphilis the antilipidal antibody often exists alone. This work was confirmed by Puccinelli and Oddo (Gio ItalD 87: 447 1946) who described the technic of demonstrating the 3 antibodies.

Convincing evidence of the existence of specific antitreponemal antibody in syphilitic serum is seen in the work of Nelson and Mayer (JExperM 89: 369 1949). Employing the virulent Nichols strain of *T pallidum* kept alive on a special basal medium, they showed that these actively motile spirochetes lost their motility when incubated at 35 C. for 16 hours in the presence of syphilitic serum. No such immobilizing effect was observed with normal and with false positive control serums. They demonstrated furthermore that immobilizing antibody is distinct from antilipidal antibody; after adsorption with lipidal antigen of all the reagin of a syphilitic serum, so that the filtrate gave negative flocculation and complement fixation reactions, the immobilizing effect of the serum remained unaltered. The same specific immobilizing antibody is present in the spinal fluids of patients with untreated neurosyphilis. The antitreponemal antibody appears to be truly specific of *T pallidum* infection.

Evaluation of Serologic Tests.—Interpretation of laboratory reports requires considerable knowledge of serology. Reliability of a laboratory depends to some extent on the volume of work done, meticulous adherence to standardized methods, and frequently repeated checking with other good laboratories. It is fundamentally a mystery why a lipid extract of tissues of a normal animal reacts with the serum of a syphilitic human being and it is true that the serums of some nonsyphilitic persons, as well as the serums of some persons suffering with diseases other than syphilis, give syphilitic reactions on testing. The biologic false positive cannot by classic means be distinguished from the truly positive (Rein and Elsberg JID 6 113 1945) although complex procedures investigated by Neurath et al. (AmJSyph 31 347 ff 1947) made it hopeful that the puzzle might be answered. See Treponema immobilization test (p 430) Antibodies in syphilis (p 433)

See Cumming et al (J 110 1943, 1935) evaluation of tests in U.S.A., Committee Rept. (VDI suppl. #1 1938) Parran et l. (J 109 422, 1937), stat laboratories Binkley (OhioSMJ 35 731 1939) interpretation of reports, Kolmer (AmJPubH 34 510, 1944), advises use of more than 1 test and repeated tests; Rein (NYSJM 47 2480, 1947) the higher the total dose of penicillin and the longer the time during which it is given, the shorter the time required to attain seronegativity.

QUANTITATIVE TESTING is becoming routine, early encouraged by Moore and Eagle (AnnIntM 14: 1802, 1941). When a low titer persists after adequate treatment, no further

treatment is indicated unless the titer rises significantly according to Thomas (AmJSyph 30 317 1946) Clinical relapse is regularly heralded by rise of titer Persisting high titer after presumably adequate treatment may justify continuation of therapy In neurosyphilis, the spinal fluid findings, not those of the blood, are the reliable guides. Variation in titer is puzzling especially in low titer patients, where a test may be negative at one time and weakly positive at another this is sometimes due to variations in the sensitivity of the test (Mohr and Smith AmJSyph 4 122, 1940) Extremely sensitive tests give more false positives but miss few actual cases, and less sensitive testing technic yields positives more to be trusted but misses some weakly positive cases (Tuft and Richter: AmJSyph 23 31 1939) Test technic was described in detail for several standard tests in VDI Suppl. 9 1930 Hi richsen (VDI Suppl. 14, 1941) reviewed the subject in detail. The anticomplementary test sometimes means the titer is extremely high (Carter: ADS 46: 842, 104) Discrepancies between results of testing the same serums with different tests were studied in detail by Mahoney (NYBJM 43: 843 1943)

The demand for quantitative serologic testing increased markedly following the development of rap d therapeutic measures for the treatment of syphilis with penicillin. It must be pointed out, however that a quantitative serum test i not necessarily an aid to diagnosis. It determines only the maximum dilution in which that particular serum still gives a pos tiv reaction. A syphilitic patient whose serum is positive in a 1 16 dilution is no less syphilitic than the one whose serum is positive in a dilution of 1-256.

Too much emphasis has been placed, in routine qualitative testing on the pseudo-quantitative method of reporting positive reactions as 1 plus, " plu , 3 plus and 4 plus. The physician is often lulled into a sense of false security on serologic recheck if the laboratory reports a reduction in titer from 3 plus to 1 plu and he and the patient may be unduly concerned if the report changes from a 1 pl s to a 3 plus reaction. Furthermore a 4 plus reaction does not necessarily indicate a strongly positive reaction since one 4 plus serum may be positive only in a dilution of 1: whereas another 4 plus serum may continue to give positive reactions in a dilution of 1 .56 The latter serum was 128 times more positive than the first serum, yet both we e reported as 4 plus or strongly positive by the routine qualitative method.

The value and importance of carefully performed and properly interpreted quanti tat ve tests cannot be overemphasized. Unfortunat ly th re has been a great deal of confusion regarding the p esent tatus of quantitative procedures because of the dis sim lar methods of performance interpretation and reporting of the tests.

The chief value of quantitative tests lies in the fact that the physician can by their use ad antageously evaluate the serologic response of his patient to a particular treatment schedule from the onset of therap throughout the period of clin cal a d serologic follow p. A reduction in serologic titer may be the only clue and a valuable one as to the success of antisyphilitic therapy

Carefully performed and prope l interpreted quantitative tests are of value to the pract ci g physician in the following ways

(1) To est mate response t treatme t. Short xtend e method of therapy es pecial with pen c llin, are completed while the pat ent is still seropos t ve If serologic tests are to contribute in determining the efficacy of therapy quant tati e procedures performed at regular mo thly ntervals are eces ar If quant tati e tests rema n strongly pos t ve long after reversal to seronegativ ty m ght be anticipated, one may judge the case a treatment fail re although there are various factors wh h infl ence th t me requ red to attain se onegativity

( ) To diff rent t between se ologic relapse and rei fection.

(3) To diff rentiate between pren tal syph lis and passive reagi emia.

(4) To determine reagin fastness (seroresistance)

(5) To d fferentiate between true and false posit v serologic reactions for syphilis

Limitations of Serodiagnostic Procedures for Syphilis.—It is true that most of the positive serologic reactions obtained with currently used non-specific lipid antigens are due to syphilis. It is also true that positive results occurring in some normal individuals are unrelated to syphilis and represent a general biologic phenomenon. False positive nonspecific reactions may also occur as the result of a variety of infectious diseases, immunizations and metabolic disturbances. Not infrequently when false positive reactions have occurred in the absence of syphilis, persons have been stigmatized and given treatment solely on the basis of positive reactions disclosed by routine serologic examinations. Compulsory preinduction prenatal and premarital serologic examinations and the increasingly widespread use of routine blood testing in medical practice in industry and on separation from the Armed Forces increased the number of individuals needlessly subjected to antisyphilitic treatment

Serodiagnostic tests are not truly specific for syphilis so that the physician must be aware of conditions other than syphilis which may produce nonspecific, nonsyphilitic reactions.

FALSE POSITIVE REACTIONS may be either technical or biologic

Technical false positives may occur with serums containing no antibodies and may be due to (1) technical errors in the collection and labeling of specimens (2) the use of unsatisfactory contaminated or hemolyzed blood specimens (3) errors in the performance of the serologic tests (4) the use of faulty materials and reagents in the test or (5) errors in recording or reporting the final results. With the improvement of serologic technics and the use of improved materials especially purified antigens of the cardiolipin type there has been achieved a marked reduction in the incidence of technical false positives.

Biologic false positives may be due to (1) the presence of antibody like substances similar to the antibodies produced in syphilitic diseases; (2) an increase or alteration of the seroglobulin fraction or (3) an increase or alteration of some other chemical substance or substances in the blood.

False positive tests may sometimes be avoided by requesting several different procedures on the same serum by different laboratories. One never diagnoses syphilis on the basis of the report of one test

When the test is positive because of the existence of nonsyphilitic disease the positivity is as a rule transient, lasting for only a few weeks or months, and as a rule the titer is not high. Disorders which induce pseudosyphilitic positivity include upper respiratory infections vaccination against smallpox infectious mononucleosis, typhus, filariasis, hyperproteinemia, varicella injections of foreign protein such as tetanus toxoid, infectious hepatitis, malaria leprosy tuberculosis, lymphopathia venerea leishmaniasis and scarlet fever Syphilitic reaction occurs in yaws pinta rat bite spirochetosis, relapsing fever and other spirochetal infections. Before interpreting tests as indicative of syphilis, consideration must be given these possibilities (Mohr et al. AnnIntM 77 332, 1946 Beerman AmJMSc 209 525 210 524, 1945 Albrecht CurMDig July 1947 Stokes et al. J 130 57 1946)

See Hasen et al. (ADS 37 431 1938) in malaria Parran and Emerson (VDI 1: 1 1939), in tuberculosis Baduak (J 112 1462, 1939) in mononucleosis; Lynch et al. (J 117 591, 1941), in vaccinia Mohr et al (AIntM 68: 898, 1941) 1 normal persons; Cardon et al (ADS 46 712 1942), in hyperproteinemia; Kahn (JLabClinM 28: 1175, 1943) verification; Kissell and Puccinelli (BullUSAMD Sept. 1944, p. 3) in jaundice, Faust and Ross (VDI 25 173, 1944) in leprosy, more often in lepromatous than tuberculoid; Eager and Moffat (VDI 25 271, 1944), familial; Helmoff (MilSurg 95, 419 1944) after tetanus toxoid Kane and Henneman (NEngJM 233 407 1945), in varicella, Lofgren (ActaD-V 26 241, 1946) in erythema nodosum Page and Helmoff (AnIM 73 181, 1946), 100 instances; Rein and Kent (J 133 1001 1947), 1 malaria, Singer and Boerner (AmJMSci 214 89 1947), familial, Karafonetis and Kent (JLabClinM 43 243, 1954), in infectious mononucleosis Ahlson and Dick (*Lancet* 2 364, 1954) in virus pneumonia *Portnoy and Edmundson (InternatJLepr 22* 181, 1954) syphilitic serum from patient with or without leprosy shows increased reactivity if choline chlorid is added to antigen suspension, but choline diminishes reactivity of false positive serum from leper

Acute and chronic types of biologically false positive reactions may be distinguished (Moore and Mohr: J 150: 467 1952) The former are associated with various infections and are transitory The latter may signify the presence of serious underlying disease sometimes of the collagen type, and every effort should be made to follow the patient and determine the cause. False positive serologic reactions may precede other symptoms identifying systemic lupus erythematosus, and in fact may foreshadow this dread disease (Haserick and Long: AnnIntM 37 559 1952) A false positive reaction for this reason alone necessitates painstaking investigation.

Many normal animals give positive tests (Kemp et al.: AmJSyph 4 537 1940) Biologic false positivity life-long when it occurs in normal human beings, has been difficult to identify by serologic methods (Scott et al. AmJSyph 29: 505 1945)

The treponema immobilization test generally gives negative results in biologically false positive reactors and constitutes a significant procedure for distinguishing syphilitic from nonsyphilitic individuals (Mohr et al.: AmJSyph 34: 405, 1950)

Persistent positivity perhaps justifies the giving of adequate treatment now that penicillin makes such a recommendation less hazardous to the patient than this advice would have been a few years ago. In pregnancy the evaluation of positive reactions is less conservative for the fetus must be protected possibly at the cost of giving unnecessary treatment to some women (Stokes and James: AmJSyph 33: 14 1949) Persistent positivity alone and not corroborated by clinical or other evidence of the disease or by positive reaction with a specific treponemal test, does not justify the diagnosis of syphilis.

ACUTE FALSE POSITIVE REACTIONS.—*Since the large majority of false positive reactions are of the transient type,* reverting to seronegativity within a short time and due to any of many possible nonsyphilitic conditions in susceptible serologic reactors, all individuals with *positive serologic reactions* for syphilis whose apparent infection is unconfirmed by history or clinical evidence should be followed serologically without treatment for 3 months, serologic tests being performed at intervals of from 2 to 4 weeks. Then the patient should be completely reappraised in an effort to ascertain whether syphilis is present. Continuing diminution of serologic titer in a relatively short time without antisyphilitic treatment, is strong evidence favoring interpretation of serologic reactions as nonspecific. Irreparable harm can be done by ill-considered hasty diagnosis. If treatment is started prematurely the evidence which could finally lead to an accurate diagnosis will be obscured. *Serologic tests become negative after a few injections,* so that one never knows whether the reversion to seronegativity represented response to therapy or merely reflected the fact that the patient was not syphilitic.

CHRONIC FALSE POSITIVE REACTORS AND THE PROBLEM OF DIAGNOSING LATENT SYPHILIS.—Physicians are occasionally confronted with individuals in whom routine serologic examinations reveal positive serologic tests for syphilis uncorroborated by any other evidence of the disease. The patient is not likely to be subjected to all the procedures required to establish or exclude the diagnosis of syphilitic infection but is likely to receive penicillin therapy in preference to a necessarily time-consuming and relatively expensive investigation. The importance of serologic and clinical follow up after such therapy is generally not stressed for one may fail to realize that once treatment has been instituted the individual *must be considered* as probably syphilitic and *therefore entitled to the same follow up as if he had been proved to be syphilitic* (Rein and Elsberg AmJClinPath 14 461, 1944).

The existence of specific antitreponemal antibodies in the serums of latent syphilitics by means of the immobilization phenomenon has been proved by Nelson and Mayer (JExperM 89 369 1949). Whenever possible a diagnosis of latent syphilis should not be made until these specific antibodies have been demonstrated. The TPI test approaches absolute specificity in nonsyphilitic patients, having proved negative in 99.7% of almost 1 400 of them tested by Zellman (AmJSyph 38 506 1954). The degree of positivity of this test increases with the duration of infection.

SEROPOSITIVE *REACTORS* SHOULD BE *CAREFULLY INVESTIGATED in an attempt* to establish or exclude a diagnosis of latent syphilis prior to therapy

(1) Whenever possible demonstrate the presence of specific antitreponemal antibodies *by means of the immobilization phenomenon. A biologic false positive reactor* may be correctly identified even after and in *spite of* antisyphilitic treatment.

(2) Withhold therapy *for* from 3 to 6 months in *order* to afford the transiently false positive patient an opportunity to revert spontaneously to seronegativity

(3) If adequate work up is not feasible due to lack of facilities or poor cooperation of the patient penicillin therapy should be administered to prevent the possibility of the development of late syphilitic sequelae

(4) Once therapy is administered the patient should be considered as a latent syphilitic and should have the benefit *of the same follow up as is due a patient known to have* latent syphilis

FALSE NEGATIVE REACTIONS.—A serious limitation of serodiagnostic procedure *is the occurrence of false negative reactions.* When the serum of a patient with clinical syphilis gives a negative reaction that patient is said to have seronegative syphilis, and the reaction is interpreted as falsely negative. Actually the serum contains so little reagin that the test failed to detect its presence. If the same serum were rechecked by a more sensitive test there might result a positive reaction. Such discrepancies are frequent in patients with primary syphilis. After the development of a primary lesion, the serum may give *negative reactions with insensitive tests for a week* or longer, yet with more sensitive tests positive reactions may be obtained within a few days

after the appearance of the chancre In an unpublished study of experimental syphilis in rabbits, Rein found it possible to detect the evidence of syphilis by means of a sensitive serologic test as early as 5 days before the clinical appearance of the chancre. This suggests that although antibodies begin to appear in the blood soon after inoculation with *Treponema pallidum*, routine tests are not sufficiently sensitive to detect their presence. The incidence of seronegative primary syphilis depends then not only on the time elapsed since inoculation but also on the sensitivity of the tests employed.

Similarly in seronegative late syphilis, as exemplified not uncommonly in patients with syphilis of the aorta (there are reports that the incidence of seronegative cardiovascular syphilis and neurosyphilis is as high as 40%) seronegativity results from the relative insensitivity of the tests used. When the more sensitive tests are used the incidence of negative reactions markedly decreases. Thus the number of cases of seronegative late syphilis does not depend wholly on the biologic course of syphilis but rather on the sensitivity of particular tests. Yet even with the most sensitive tests available one may obtain a negative reaction in a patient who has syphilis.

Seronegativity in the presence of syphilis may be due to several factors (1) the amount of antibody is minimal and cannot be detected by tests of ordinary sensitivity (2) so much antibody may be present that false negative zone reactions occur (3) if fresh serum is used, containing considerable amounts of thermolabile-inhibiting substances, the test may be negative and (4) the presence of a thermostable-inhibiting substance in the albumin fraction of the serum may result in negative reaction.

Serologic Response in Penicillin-Treated Syphilis.—Some physicians are disappointed when serologic tests remain positive fo several months or more following penicillin therapy Several factors, however influence the time required to attain sero egativity (Rein: NYSJM 47 450 1950):

(1) State of Disease.—The olde the disease and the longer the spirochetes have been present the longe it takes for the host tissues to stop formi g antibodies. As a rule patients with secondary syphilis require more time to become sero egative than patients with seropositive primary disease.

(2) Immunologic Responses of Individual Patients Related to Serologic Titer.—Some patients with syphilis develop more ant bodies than others. As a rule, patients with high serologic titers at the onset of therapy require more time to attain seronegativity than those with relatively low titers.

(3) Sensitivity of the Serologic Procedure.—The more sensitive the serologic test, th longe it takes to attain seronegativity a measured by it. Whe one employs battery of serologic tests with various sensitivities, negative reactions may be obtained with the less sensiti e tests long before more sen itive test become negative

(4) Type of Test.—Certain types of tests m y remain positive long after other tests have become negative even though they may be of comparable sensitivity

It must be pointed out that th re are many variations in these factors, and no fixed rules can be made regarding the time required to attain seronegativity It is generally agreed that the persiste ce of positive serologic reactions does not necessarily indicate the persistence of act e syphil tic infection, and that it is not necessary to retreat patients merely because they may not have reverted to seronegativity soon afer completion of therapy

The pattern of return to seronegat vity as determined by applying a battery of 7 tests to 100 patients with primary syphilis and 100 with secondary treated with penicillin, wa studied by Cutler et al. (AmJSyph 37 514 1953) Reversal was faster follow ng treatment f primary syphilis than of secondary and sensitive tests were slower to revert than relatively insensiti e o es. Individual patterns of response were seen which were quite variant from the usual patterns.

Prognosis.—The earlier treatment is instituted and the more thoroughly it is carried out the better the outlook in general. Clinical cure of the infection, but not of its scars and their mechanical and physiologic sequelae, can nowadays be expected with confidence The consequences of undetected and untreated disease are as disastrous as they ever were and it could at one time have been said that the consequences of the disease were disastrous be-

cause of the treatment in the days of mercurial and arsenical therapy In tolerance of penicillin, too has taken its relatively small toll and must be given due consideration.

Failures of adequate treatment to eliminate the causative organism are *nowadays extremely unusual, and many of the "failures" are in fact rein* fections. The individual who acquires syphilis, unless it is an innocent infec tion, is usually the type of person who is likely to expose himself again. It does no good and perhaps provokes psychologic trauma to tell the patient this, yet it is difficult to erase the moral stigma associated with syphilis (JMoSMA *34 467 1937 35 65 1938)*

Alcoholism tobacco and mental physical and sexual excesses are detri mental to the welfare of the patient The location of the initial lesion exer cises no influence upon the aftercourse of the disease. In patients whose syph ilis is adequately treated the probability of late complications is greatly di *minished.*

The disease may materially lessen life expectancy in men with acquired syphilis this was shortened from that of the general population in the age group 30 to 60 years by 17% in the white and by 30% in the Negro Usilton and Miner (VDI 18 231 1937) reported from their study of Cooperative Clin ical *Group material Between 1939 and 1948 the total syphilis mortality rate* was reduced approximately 47% (Usilton et al AmJSyph 37 403 1953) Mortality was relatively greater among males and among nonwhites. Of the total syphilis deaths, cardiovascular syphilis in 1948 represented a much greater proportion than in 1939

Review of actuarial studies by Schamberg (AmJSyph 30: 540 1946) showed that the best figures indicated that even the well-treated group had an appreciably higher mor tality a fact probably due to factors of selection. Schamberg concluded, "There is no evidence that syphilis adversely influences life expectancy except through the known lethal effects of its serious late manifestations in particular those of the central nervous and cardiovascular systems. There is no evidence that syphilitic infection per se or anti *syphilitic treatment predisposes to tuberculosis, pneumonia, nephritis,* or other nonsyphilitic diseases. Increased mortality in syphilitics is caused in part by death due directly to syphilis, in part to the higher death rate in segments of the population which have a high syphilis prevalence Adequate antisyphilitic treatment will in the majority of cases pre vent the late manifestations of syphilis. . . . Employers may safely hire syphilitics. The incidence of cardiovascular syphilis is inversely proportional to the amount of treat ment received in the early stages of the disease ranging from 18% in untreated cases to 0.4% in those adequately treated (*Kemp and Cochems AmJSyph 1 625 1937)* Moore and Schamberg (*J 134 1532 1947*) stated that the applicant with untreated syphilis in any stage should be granted life insurance if the applicant can demonstrate good health otherwise in all patients the spinal fluid should have been shown by adequate and reliable tests to be normal after adequate treatment and not earlier than 2 years after infection. See JVDI 27 34-52 1946.

The outlook intimately *depends on treatment. Stokes et al. (AmJMSc 188: 660,* 1934) in the Cooperative Group studies, stated that relapse diminished as the number of arsphenamine injections increased. Continuous treatment was to be preferred to inter mittent, irregular or tensive attack. Arsphenamine did not predispose to central nervous system involvement but irregular treatment certainly did. Adequate treatment (20 to 30 arsenical injections and bismuth in courses) *for* years yielded symptomatic cure of 96% of early cases, while inadequate treatment cured only 73% Any treatment is better than none yet neurosyphilis was 3 times as common in the poorly treated cases as in the untreated series.

Comparable statistics regarding the outcome in patients treated with penicillin can not be compiled for a number of years, for the drug was first used in 1943 but its striking effectiveness has been most encouraging (Moore et al. J 190 07 1944; Stokes et al. J 1?6 73 1944)

See Medico-Actuarial Mortality Investigation (Assn Life Ins. Medical Directors and Actuarial Soc of Amer N Y 1912 1914 Medical Impairment Study 1929 (Actuarial Soc Amer and Assn Life Ins Med Directors, N Y 1931) Impairment Study 1938 (id 1939) Stein et al (JSocHyg 23 258 1937) life insurance and syphilis Morgan (J 113 341 1939) Murrell and Manson (SouthMJ 32 322 1939) Statistical Bulletin, Metropolitan Life Ins Co 23 8 1942 Tait (JVDI 31 95 1950) mortality dropped from 14 in 1938 to 8 in 1948 per 100,000 Rosahn (ADS 66 547 1952) controlled experiments with populations of mice syphilis decreased longevity McElligott et al (BritJVD 29 64, 1953) deaths in England and Wales, 1931 1950

About one fourth of all patients who contract syphilis can expect spon taneous cure without treatment and another fourth achieve complete latency About one-sixth of all syphilitics who develop positive serologic tests will re main seropositive *with or without* treatment

UNTREATED SYPHILIS.—Bruusgaard (AfDuS 157 309 1929) surveyed the 2,181 patients who were given no specific treatment by Boeck who from 1891 to 1910 at Oslo preferred no treatment at all in early syphilis to the mercurial treatment then in vogue. This carefully studied untreated series served as the control in the Cooperative Group review of the effects of treatment in early syphilis. Comparison of treated with untreated syphilis (Sowder Am JS 24 684 1940) showed that (1) central nervous system relapse is 2 to 4 times as frequent in untreated cases (2) cutaneous and osseous relapses are 17 to 26 times as frequent in untreated cases; (3) treatment results in freedom from symptoms in 77% if adequate and 63% if less than adequate, while no treatment is followed by freedom from symptoms in 24 to 36%; (4) in cases of seronegative primary infection, despite treatment there occurs 1.2 to 1.5% incidence of spinal fluid abnormality within 3 to 20 years (5) adequate treatment results in freedom from symptoms in 96% while no treatment is followed by freedom from symptoms in 61% of cases in the 3- to 10-year period while in the 10- to 20-year period treatment has the advantage of 74 as compared with 50% freedom from symptoms (6) syphilis is relatively benign but it is worth treating; (7) irregularity of treatment seemed the chief cause of complications. Low dosage of arsenicals with intermittence of treatment resulted in a high incidence of neurosyphilis. Continuous treatment for 2 years cured 86% of seronegative primary cases, 64% of seropositive primary cases, and 81.5% of secondary cases. A florid secondary eruption seemed an advantage

TREATED AND UNTREATED SYPHILIS. COOPERATIVE CLINICAL INVESTIGATION AND BRUUSGAARD'S SERIES

	GROUPING BY YEARS AFTER INFECTION	INCIDENCE IN GROUPS	
		TREATED	UNTREATED
1 Relapse in the form of clinical involvement of central nervous system	*(years)*	*(per cent)*	*(per cent)*
	(3-10)	1.4	5.1
	(10-20)	9.3	16.7
2. Relapse in the form of cutaneous mucosal, and osseous lesions	(3-10)	2.0	34.2
	(10-20)	1.—	31.7
3. Symptom free cases with positive Wassermann	(3-10)	17.6	36.7
	(10-20)	*16.3*	*13.6*
[The similarity of proportions in treated (16.3%) and untreated (13.6%) cases of the 10-20 yr group suggests that about 15 per cent of fixedly positive Wassermann cases is perhaps an irreducible minimum.]			
4 Symptom-free cases with negative Wassermann	(3-10)	70	4.0
	(10-20)	63.3	36.4
5. Cardiovascular symptoms	(3-10)	0.7 1.3(?)	0 (unrecognized ?)
	(10-20)	5.8 10.4(?)	1.5
	(20-30)	?	10.0
	(30-40)	?	12.5
6. Symptom-free cases, serum positive or negative		(Adequate treatment)	(No treatment)
	(3-10)	96.0	60.7
	(10-20)	74.0	50.0

Bruusgaard's patients were restudied by Danbolt et al. (ActaD-V 34 34 1954) who were able to pick up about 20% of them. Cardiovascular syphilis was found in about 10% of them and neurosyphilis in about 6%. Some 67% of the untreated syphilitics had at no time suffered late manifestations of the disease.

Autopsies of 380 untreated syphilitics revealed anatomic lesions of syphilis in 39% and no such lesions in 61% while 23% of the series died as a result of syphilis, a death rate approximating that of Bruusgaard's series, as reported by Rosahn (JVDI 27 293 1946). Some 17% of these persons had achieved spontaneous cure without treatment.

Untreated Negro males, 231 cases followed for 16 years were reported on by Pesare et al. (AmJSyph 34 201 1950). There was a higher mortality rate

in each 10-year age group than in the controls. There was a higher incidence of potentially disabling conditions of heart, aorta and other parts of the body until age 55 was attained.

Toxic reactions to medication probably do not affect the status of the disease favorably or unfavorably except in so far as they may signify that it is impossible to use a particular drug.

Prophylaxis.—Avoidance of exposure to *S. pallida* can be depended on to prevent infection. Yet the admonition to avoid exposure is futile, for the human herd is promiscuous. It is generally possible to prevent infection despite a syphilitic contact if advantage is taken of the antiseptic effects of the prompt and generous use of soap and water followed by diligent application of Metchnikoff's paste composed of 35 to 50% calomel in hydrous wool fat and petrolatum. The Army prophylactic kit, a single tube containing 30% calomel and 15% micronized sulfathiazole achieved a failure rate of 0.13% (BullUSAMD 76: 25 1944). Mechanical separation of presumably infected tissues from those to be kept pure is probably best (Cautley et al.: AmJMSc 195 153, 1938). Moist sores teeming with spirochetes are not regionally limited to genital distribution.

The maintenance of an adequate level of bismuth by injecting a suspension of it into prostitutes every 2 weeks may keep them noninfectious (Hanzlik et al.: AmJSyph 24 465 1940).

If the possibility of infection has been incurred, and the time for prophylaxis has passed, one does not know whether inoculation has actually taken place. In such cases, abortive treatment comprising 900,000 units of repository penicillin 0.05 Gm. Mapharsen and an intramuscular injection of bismuth, all in one visit, prevented the development of syphilis, according to Alexander and Schoch (ADS 59: 1, 1949). They argued that waiting for a definitive diagnosis is outmoded, yet it seems highly desirable to know whether the patient was infected or not. See Treatment penicillin (p. 44)

See Stokes (BJD 48 57 1936 VDI 23 193, 1942) Hazen et l. (J 115 1185, 1940) condom, soap and calomel ointment Eagle et al. (AmJSyph 31 25 , 1947) arsenoxid ointments Edit. (J 139 925, 1949) oral penicillin frowned upon, although it works (Eagle et al. PHRpts 63 1411 1948)

Control.—As a public health problem, syphilis has been attacked with vigor in the United States. Heller (AmJSyph 31 569 194) estimated the death rate at 16 per 100,000 in 1936 and estimated it as 9.2 per 100 000 in 1946, while infant deaths from syphilis dropped from 69 to 25. He quoted as basic the 9 principles of control advocated by Parran: provision of an adequate and adequately trained public health service staff, case finding and case holding premarital and prenatal serodiagnosis, provision of free diagnostic services, provision of treatment facilities distribution of drugs for therapy routinization of serodiagnostic tests, the dissemination of scientific information, and public education. The efforts of the New York City Health Department were similar and effective as described by Rice (AnnIntM 12 503, 1985)

Case finding and case holding, the tracing of contacts and inducing patients once gotten under treatment to persist in treatment were discussed by Woods (VDI 20 3 1 1939). Practical problems were reviewed by Stokes (AmJSyph 23: 549 1939). Contact tracing can be worth while and successful (Casselman and Cadwallader VDI 20 153, 1939). While professional prostitution is relatively unimportant statistically, it must energetically be suppressed, it is generally agreed (Clark VDI 21 349 1940 Stokes VDI 23 193, 193 194 ; Williams CanadPHJ 31 461, 1940). Amateurs of the civilian public were the greatest hazard to the Armed Forces. Contact tracing sustained by quarantine authority can disclose numerous infectious individuals and bring them under treatment (Freeman OhioSMJ 36 616 1940).

Rapid treatment centers established during the war emergency and most creditably managed in the United States by Wile contributed greatly to the control effort. The risks of intensive treatment as then practiced led Stokes (J 1 0 1093 194) to question the wisdom of dangerously rapid treatment in dealing with the latent cases comprising some 0 to 50% of the total cases uncovered by diligent case finding. See p. 449

An especially remunerative method of case finding is the serologic testing of large groups of individuals (Anderson et al. J 120 8 3 194 . Smith and Gill (SouthMJ 43 183 1950). There has been a marked reduction in the numbers of cases so found. Nevertheless Syphilis is still with us and case finding by routine STS in industrial groups should be persisted with, stated Downing (J 153 465 1953) who pleaded for expertness in evaluating employees found to react positively.

Premarital blood testing is in general favor and succeeds in reaching large numbers of persons (Kolmer: J ILL: 2353 1939) although it has been argued against (Nelson AmJSyph 23 58, 1939 see p. 336). Recognition is universal that serologic tests during pregnancy are essential and that congenital syphilis is a preventable disease (Hogan NYSJM 37 929 193) see Pregnancy and syphilis (p. 44). Prenatal treatment (p. 466

Case holding has become less problematical since penicillin therapy has so markedly reduced the duration and simplified the treatment of syphilis, the mortality of which is steadily diminishing (Wright: J 140: 8, 1951). Yet the disease is not defeated merely

by effective treatment, and the aim of global control is far from achieved although the realization of such a goal can no longer be considered fanciful (Moore AmJSyph 15 101, 1931)

See Smith and Brumfield (J 161: 1955, 1933) contact tracing Vonderlehr (J 107: 782, 1936) epidemiology; Nelson and Crain (Syphilis, Gonorrhea and the Public Health, Macmillan, 1938); Stokes and Ingraham (J 113 1132, 1939) syphilis and the law Packer et al. (VDI 23 289 1942) follow-up of delinquents from treatment; Sweeney (VDI 23 137, 1942) contact tracing, Frost (JVDI 29: 41 1948), case holding in VD clinic (VDF ct Sheet, DI VD Office of Statistics, USPHS, #6, 1949) estimated incidence 1936-1949 case rates, mortality epidemiologic data, costs, results of penicillin therapy; Marcussen and Bendal (AmJSyph 34 144, 1950) epidemiology in Greenland Willcox (BMJ 1: 677 1953) syphilis and marriage.

Marriage should be undertaken by a syphilitic person only after he has undergone a complete course of adequate treatment and after he has remained free from evidence of the disease for a considerable period after the termination of active therapy Perhaps 2 years and preferably more should have elapsed from the time of infection. When the infection was 5 years old at the time of marriage 30% of the partners became infected, but after the tenth year the likelihood of the normal partner s acquiring the disease was almost nonexistent (O Leary: PSMMC 15: 1 1040) See Jones (JMoSMA 36 196, 1939) It is probable that the estimate of the waiting time t be recommended would be considerably shorter than 2 years if modern treatme t were pursued energetically

Conjugal neurosyphilis was studied by *Hutton (JMentalSci 87: 315, 1941)* whose observations supported the theory of a neurotropic strain of *S. pallida*. The marital partner of a known syphilitic must of course, being the most intimate contact, be carefully investigated.

Surgery in the Presence of Syphilis.—In undertaking surgery upon syphilitic individuals there is a real but small risk of acquiring syphilis by accidental inoculation (*QMN: J 133: 625 1045*) *As for the patient, there is an ideal focus for the development* of acute syphiloma in a surgical wound. In preparation for operation 2 or 3 doses of arsphenamine and of bismuth in a period of 2 weeks were known to suffice to protect against untoward results (Wile CalWM 49 7 1938; Wiltrakis et al.: IllMJ 79: 141, 1941) Penicillin should be used.

Tuberculosis does not contraindicate the treatment of concomitant syphilis, unless the *medication schedule is too intensive* (QMN: *J 124: 308, 1944*) *Penicillin is well* tolerated and efficient. There was a higher than normal incidence of tuberculosis among the Negro syphilitics in the clinic of Goldblatt (ADS 40 792, 1939) possibly to be explained on sociologic grounds. The tuberculous patient with syphilis needs and benefits from antisyphilitic treatment. See Warring (AmRevTuberc 40: 175, 1939)

Diabetes accompanied by syphilis was studied by Parkin (A IntM 31 27* 1944) When 19 such patients were treated for syphilis, their diabetes improved. There seemed to exist a relation between syphilis and gangrene occurring in mild diabetics. It is doubtful that syphilitic diabetes occurs, however (McDaniel et al. AIntM 66: 1011, 1940)

Treatment of Syphilis.—See articles on particular drugs in chapters on Treatment and Dermatitis medicamentosa. Syphilis has often indeed been mistreated. Classic but dated reviews of treatment emphasizing need for prolonged and continuous therapy are those of Stokes and Usilton (ADS 35 377 1937) Moore et al. (J 116 2405 1941) Padget (AmJSyph 24 692, 1940) and Cole (J 117 1001 1941) See Moore (Penicillin Treatment of Syphilis, Thomas, 1946)

One expects nowadays to eradicate spirochetes from an infected person who may or may not suffer significant cicatricial damage leading to injurious sequelae. The cured patient with scars aneurysm or demented brain still requires medical care. Some syphilitics suffer deleterious psychologic effects from knowing they have been infected, and the psychiatric aspects of such individuals, possibly organically unharmed by the disease that has otherwise been cured, comprise a real and challenging medical problem.

External Treatment.—Cleanliness and hygiene are important. In mixed infections with both *T pallidum* and *H ducreyi*, local treatment is as for chancroid. Cauterization or excision of a chancre is futile. Nonulcerative syphilids require no local treatment Ulcerative or pustular lesions may be covered with poultices moist with 1 8,000 bichloride of mercury solution or 2% ammoniated mercury ointment The cutaneous manifestations of syphilis are so promptly responsive to penicillin therapy that as a rule they require no local treatment at all. Ulcers in a syphilitic patient may be due to streptococci, carcinoma or other diseases, just as in nonsyphilitic individuals.

PRINCIPLES OF TREATMENT—Best treatment of early syphilis in the prepenicillin era entailed (1) early correct diagnosis (2) the use of drugs of proved worth (3) continuous treatment *without rest periods* (4) *a treatment* period of an arbitrary minimum of 12 to 18 months (5) determination of cure ' only by lifelong posttreatment observation and (6) the avoidance of poisoning the patient (Moore AnnIntM 10 30, 1936) Continuous therapy *the injections being given at regular intervals without rest periods*, The American System, is believed to be best The duration of the period during which chemotherapy is actually administered is considerably diminished with the use of penicillin. Treatment must be purposeful individualized and carefully planned and executed The patient must be brought to trust his physician and to cooperate intelligently and willingly

Treat the patient not his blood (Moore) When a patient has latent syphilis and has received adequate treatment he should be let alone except for periodic titered serologic tests and checkup physical examinations. One must remain continuously aware of the hazards of any therapeutic agents used seeing to it that the treatment is not worse than the disease A large proportion of syphilitic infections are comparatively benign and harmless. Mental and physical breakdowns have been precipitated by persistence in misguided therapeutic measures, overtreatment being responsible for depression, *emotional instability fatigue weakness, loss of weight and nervous irritability* (Cormia CanadMAJ 40 445 1939)

Clinical cure is usually achievable and the patient should be given encouragement and reassurance (Moore AmJSyph 22 648 1938) While almost all physicians treat syphilis, *few are syphilologists. A wise physician is humble admits his doubts to himself and takes advantage of consultation with experts.*

DURATION OF TREATMENT—*It was once thought proved that few cases of* syphilis are cured before the end of 1 year and that the majority require at least 2 years of active medication. American practice sustained by evidence collated by the Cooperative Clinical Group insisted on the continuous method of treatment with no rest periods. *If* no clinical evidence of the disease was to be found after 18 months of treatment a 6-months vacation from medication was taken and then serologic tests were made

Titered serologic estimations are particularly instructive If examination proves negative after 6 months, a further rest of 6 months is taken, provided always that no reinfection is manifested and a second examination is made If still negative a further rest of 6 months, and a third test A year later a final examination is made *If* any of the analyses are positive treatment is reinstituted.

With speedier methods of treatment the old standards have required revision. *Following a treatment period ranging from a few days to a few weeks* in duration, titered serologic tests should be made monthly for a year then at lengthening intervals. If the serologic titer remains zero or low and if the spinal fluid remains normal or of inactive formula and if the cardiovascular examination including *fluoroscopy is normal and if 5 years have elapsed* since the termination of treatment the patient may be judged cured

Spinal fluid is often abnormal when the blood ceases to show evidence of the disease Asymptomatic neurosyphilis is a great danger to the patient, for it is manifested by no abnormality whatever in the clinical examination, yet presages progressive neurosyphilis and the worst results that syphilis produces.

PREGNANCY—*Treatment of 116 women during pregnancy with* Mapharsen and bismuth was followed by 94 7% live births in the 76 patients who received 6 or more doses (Castello et al AmJSyph 23 332, 1939) *Danger of severe reactions among pregnant women treated intensively with arsenicals is greater than is generally realized* (Ingraham J 112 1037 1939) The pregnant woman is not exempt from any of the more severe types of reaction of in

tolerance including fatal hemorrhagic encephalitis, acute circulatory collapse hepatic damage, dermatitis and aplastic anemia Treatment of syphilis during pregnancy does not increase the liability to toxemias of pregnancy (Peckham AmJSyph 25 280 1941; J 117 1863 1941)

It is essential that all seropositive pregnant women receive treatment in order to prevent prenatal syphilis.

The effectiveness of penicillin and its safety in pregnancy render out-of date the studies of the use of less modern drugs. Penicillin can be used successfully late in pregnancy if the child is still viable (Cole et al.: ADS 54 255 1946) It should be used routinely (Goodwin and Moore J 130 688 1946) See Congenital syphilis, prenatal treatment (p 466)

NEUROSYPHILIS AND EARLY TREATMENT — Asymptomatic neurosyphilis was found in 13.5% of 5,300 patients of O'Leary et al. (ADS 35 387 1937) Adequate treatment of early syphilis was followed by an incidence of spinal fluid abnormality of 7.5% and irregular treatment by 22.6% Of those with abnormal spinal fluid 14% had negative blood tests. The less the degree of spinal fluid abnormality the better the response to therapy proved to be If treated syphilis remained latent the spinal fluid remained so in 99% of the cases. Serologic relapse warrants another examination of the spinal fluid Seroresistance of 4 years duration or more was associated with 75% incidence of central nervous system involvement. Penicillin therapy of early syphilis is followed by a notably low incidence of neurosyphilitic relapse

FAVORABLE RESPONSE TO THERAPY is measured by disappearance of spirochetes from sores, healing of visible lesions, diminution of titer of quantitative serologic tests, improvement in the spinal fluid formula manifestations of well-being of the patient such as gain in weight and in ability to perform mental and physical work which syphilis handicapped prior to its treatment and relief of symptoms of the myriad varieties for which syphilis may be responsible Quantitative serologic studies (Belding AmJSyph 24 29 1940) showed that chemotherapy reduced the titer in about a third of the cases of late acquired syphilis and half the cases of congenital syphilis arsenicals reduced the titer twice as much in early syphilis as in late.

One should not be stubborn in attacking the blood test for at least 15% of all syphilitic positives remain so no matter what is done The absence of necessity for reversing serologic tests must be explained to the patient if he falls into this unfortunate group who are frequently subjected to overtreatment its hazards and its costs, and who frequently develop syphilophobia. See Latent syphilis (p 409)

It is likewise inadvisable to push treatment unreasonably in cases of neurosyphilis, in which a positive STS was found to persist in some 84% of those followed for 5 years and in 70% of those followed for 10 years by Thomas (J 153 718 1953) He found furthermore, positive tests for reagin in the spinal fluids of 63% of patients followed for 5 years and 28% of those followed for 10 years after treatment Fluctuations in results of tests proved to be a curious phenomenon, but *relapse of neurosyphilis as determined by* increases in CSF cell count and other quantitative tests never occurred later than 2 years after treatment had rendered the infection inactive Whatever the explanation may be for the bizarre serologic patterns noted in a prolonged follow up of treated syphilitic patients, it is reasonably certain, Thomas concluded, that, in the absence of other evidences of relapse or progression of the disease they do not indicate continued activity of the syphilitic process, and treatment should not be continued solely on the basis of such serologic patterns.

See Serodiagnosis, evaluation of tests (p. 413)

UNFAVORABLE RESPONSES TO THERAPY include dermatitis medicamentosa (q v) the Jarisch Herxheimer reaction therapeutic paradox resistance to treatment and relapse Reinfection when it occurs—and this is not seldom—represents a good therapeutic result in the original infection upon which a new infection is superimposed

THE JARISCH HERXHEIMER REACTION is a temporary inflammatory aggravation of the symptoms, which usually occurs following the first administration of spirocheticidal drugs. It is attributed to enhancement of allergy by the killed spirochetes. This sudden symptomatic flare is to be avoided when the optic nerve, auditory nerve or aorta is involved for the results of vigorous *treatment may be extremely harmful*. See *Dermatitis medicamentosa* p 172. See excellent study of Farmer (J 138 480 1948). The reaction is provoked especially when the active spirocheticides, penicillin and Mapharsen, are used. It was apparently produced by the injection of immune serum into rabbits with experimental syphilis, a phenomenon of hypersensitization (Sheldon et al AmJSyph 35 405 1951). Benadryl did not influence the phenomenon, according to Stewart (ADS 60 427 1949) and ACTH does not prevent it (Heyman et al. BJVD 28 50 1952). It is not related to histamine.

It occurs in about 40% of patients with early syphilis and in from 60 to 80% of neurosyphilitics started on penicillin (Heyman et al). The rate of occurrence was 48% in early congenital syphilitics treated with penicillin by Lardo and Tucker (AmJSyph 33 225 1949).

Histologically the sequence is marked by early congestion of the capillaries and small vessels. These become crowded with polymorphonuclear leukocytes, which line the vessel walls and migrate into the surrounding tissues. The *endothelium swells, the vessel walls become edematous and* the edema then disappears with subsidence of the acute phase. The infiltration resorbs and is replaced by a small number of large mononuclear cells, while eosinophiles are not increased during any stage of the reaction. The changes *are sharply confined to the syphilitic lesions. They make their appearance* within 4 hours after treatment and subside within 18 hours (Sheldon and Heyman AmJSyph 33 213 1949).

THERAPEUTIC PARADOX.—The ill effect of a curative medicine is known as *therapeutic paradox. The question was discussed by Mohr and Hahn* (AmJSyph 36 82 1952) in connection with 4 patients who developed aortic insufficiency following penicillin therapy and in spite of it. Deaths attributable to the phenomenon have been reported: a patient with gumma of the *brain died within 14 hours after the initial injection of penicillin, and an* aneurysm ruptured after 2 days, reported Scott et al. (J 139 217 1949) while a woman with pachymeningitis developed high fever and exaggeration of symptoms and died 10 days later, reported Shaffer and Shenkin (AmJSyph *34 78 1950). The phenomenon anticipated but rarely observed in cardio*vascular syphilis, is little heard of in current syphilology. One does not hesitate to give curative doses of penicillin as soon as the diagnosis of syphilis is made. See Cardiovascular syphilis, treatment.

RESISTANT CASES.—While favorable results generally follow proper treatment this does not always happen. Penicillin resistance has never been demonstrated.

Serologic resistance is a relative term, which Moore and Padget (J 110 96 1939) defined as serologic positivity in syphilis of less than 2 years duration after 6 months of continuous, prepenicillin treatment, and in syphilis of more than 2 years duration after a year of treatment. Regard must be given the sensitivity of the test. In early cases, seroresistance apparently signified that foci of active syphilis existed. In late cases, it meant merely that immunity hangs on. One sees great harm result from dogged treatment of a persistent blood test in an asymptomatic patient—asymptomatic that is until he is poisoned or has been pushed into a psychopathic state.

The percentage incidence of seroresistance is high in early involvement of the central nervous system but in late syphilis it is an integral part of latency; in fact in late syphilis seroresistance may actually be of favorable prognostic import rather than bad. The aims of treatment are to eradicate spirochetes, to heal the lesions, to relieve the symptoms, to maintain health and to prevent relapse. Serological reversal is the least important aim.

Cooperative Clinical Group figures for percentage incidence of seroresistance according to the type of syphilis were: early 10%; early congenital, 12%; meningeal neurosyphilis, 14%; tabes dorsalis, 19%; latent syphilis, 35%; meningovascular 45%; late cutaneous and cardiovascular each 50%; late visceral, 60%; late osseous, 65%; late con-

genital, 70%; and dementia paralytica 80% Early cases proved seroresistant in 10% under continuous treatment 35% with intermittent treatment, and almost 70% with irregular treatment.

Serologic resistance may be summarily dismissed a inconsequential after adequate penicillin therapy, for a proportion in the vicinity of 15% of all patients who become seropositive remain so despite curative treatment. Resistance of the spirochete to penicillin is extremely rare if it occurs at all (Tyson JID 6: 270 1945) Cases of spirochetal resistance to arsenicals proved curable with penicillin (Noojin et al: NoCarolMJ 6: 34 1945) Treatment failures following penicillin are quite likely to be reinfections see Schamberg (AmJSyph 34: 3 1950)

Resistant cases were classed (Beerman: AmJSyph 20: 296 1936; 27: 400 1943) a those of (1) attenuated arsphenamine respon iveness, (2) recurrence under arsphenamine (3) true arsphenamine resistance in which spirochetes remain actively present in the lesions despite treatment, and (4) arsphenamine activations. Similar types of resistance to bismuth occur In combating these Beerman suggested that one might (1) change from bismuth to arsenic or vice versa; ( ) intensify treatment; (3) combine bismuth, arsenic, and iodine (4) stop treatment for a time; (5) use minor drugs; or (6) try fever lutein, or nonspecific protein while endeavoring to improve the general condition.

RELAPSE —Within 2 years after cessation of treatment most relapses which are to take place have done so. Relapses under continuous treatment occurred in 13% under intermittent treatment in 21% under irregular treatment in 45% and after intensive treatment in 41% (Cole J 107: 2123 1936) A high proportion of alleged relapses are really reinfections. Abnormal CSF does not predispose to relapse according to Sackett and Boggs (JVDI 30 219 1949) *who examined 437 patients with early syphilis who relapsed after* 2.4 million units of penicillin. Patients who received inadequate penicillin therapy and relapsed showed less abnormality of CSF than patients who relapsed after inadequate therapy previously conventional.

Chemotherapy of Syphilis.—In specific treatment, several antibiotics and metallic drugs are known to be spirocheticidal penicillin tetracycline chloramphenicol, arsenicals, bismuth and mercury Adequate treatment is usually harmless in tuberculous patients. Adequate treatment emphatically desirable is usually tolerated in pregnancy

Sulfonamides (Campbell AmJSyph 21: 524, 1937) and streptomycin (Edit.: J 131: 403, 1946) are among the drugs which are not useful in syphilotherapy

THE IDEAL ANTISYPHILITIC DRUG should possess a high chemotherapeutic rati that is, it should be of low toxicity to the human being and of high potency against the spirochete It should be easily administered and inexpensive Pe ic llin possesses all these qualities. O'Leary and Kierland (J 132 430 1946) summarized their evaluation by pointing to the f w untoward reactions penicillin prod ces, the short time needed for its administration its excellent effect on cuta eous, osseous, gastric ea ly hepatic and meningeal syphilis, and its particularly gratifying influence on the pregnant syphilitic woman, for whom it seldom fails to prevent the development of syphilis in the offspring Barksdale (SouthMJ 39 229 1946) stated, on th bas of the effect of penicillin on dark field and serologic tests, healing f lesions, and improvement of spinal fluid abnormalities It is the best drug we have ever had n the treatment of syphilis.

PENICILLIN —Four cases of early seropositive syphilis were treated with the arbitrarily selected dose and time factors of 25 000 units each 4 hours for 8 days for a total of 1,200 000 units by Mahoney et al (VDI 24 355 1943 AmJPubH 33 1387 1943) with reversal of the dark field within 16 hours and of serologic reaction in 30 to 70 days. Herxheimer reactions occurred in all, and the clinical lesions healed with notable rapidity Since their report, syphilotherapy has undergone astonishing change.

Evaluation studies were k pt ord rly by Moore and his collaborators of the Penicillin Panel of the Subcommittee on Venereal Diseases of the Nation Research Council, who controlled the penicillin available for the treatment of syphilis when the supply was limited. With the end f war and the unlimited availab lity of pure penicillin, th most various therapeutic schemes have been and are being tested. One of Mahoney' original cases underwent a gradual serologi relapse, which was rei terpreted as a reinfection, lat r (see JVDI 30 350, 1949); nd he and colleagues (J 126 63, 1944) were able to report results 1 100 additional cases: 2 instances of mild exfoliative dermatitis appeared, the average time fo serolog reversal was 70 days, patients underwent serologic relapse and it ppeared th t, as with rsenicals, certain proportion of patients fail to enjoy a curative response. Th Penicillin Panel a preliminary report (J 126: 67 1944) showed that on dosage schedules with totals ranging from 60,000 to 1,200,000 units the

relapse rate varied inversely with the dose, and that penicillin in combination with 320 mg Mapharsen a subcurative dose of the arsenical, *gave the lowest relapse rate of the* schemes tried. The excellent influence of penicillin was observed on meningovascular neurosyphilis, arsenical and bismuth resistance, and congenital syphilis in infants. Stokes et al. (J 126: 73 1944) reported on the results in late syphilis, 122 cases of 183 being neural. Gummas of skin and bone healed promptly Reagin was reduced in 50 to 60% of all late cases. Patients seroresistant with previously employed treatment methods usually improved on penicillin. Spinal fluid abnormalities improved in 4% to at least some degree the common change being a drop in cell count and total protein, so that fluids of low cell count showed comparatively little improvement Previous treatment *for neurosyphilis by older methods including fever therapy did not appear to prepare* patients for superior results with penicillin. These fundamental findings have been confirmed and elaborated by later studies.

Penicillin G is the most potent of the penicillins (Arnold et al. AmJSyph 31: 469 194) The effect of penicillin on the morphology of spirochetes was studied by Morton and Ford (AmJSyph 37: 529 1953)

The esults of a nationwide study of penicillin in early syphilis showed that the final therapeutic outcome is not related to the blood serum titer of penicillin, and that only 6 consequential reactions of intolerance occurred in 1,600 cases (Elder AmJSyph *33: 19 1949)*

Quantitative serologic tests were followed in cases of early syphilis treated with penicillin by Gustafson and Bowen (ADS 59: 303, 1949) By the end of a year 71 of 117 patients were seronegative and, of these 50% had become negative within 3 months and 91% within 6 months after treatment started. See Serodiagnosis penicillin effects (p 437)

Dubious of proof that penicillin is lastingly effective Reynolds (AmJSyph 32 233, 1948) reported treatment failure in late syphilis (including alleged drug resistance clin i al progression and recurrence of cl nical lesions) and the appearance of new lesions. A patient whose chancre remained dark field positive despite 100 000 units of penicillin q 3 h. was observed by Wexler et al. (ADS 60: 1207 1949) and Mapharsen cured this case

The Council on Pharmacy (J 136 873 1948) approving at that time a schedule of 100 000 nits each 3 hours or 600,000 unit in wax daily for 10 days stated that no proof had as yet been obtained of the existence of a strain of *T pallidum* resistant to penicillin.

Relapse during penicillin therapy apparently occurred (Cole et al. OhioSMJ 4. 595, 1946) and failures minimally of 15% when the 400 000- nit dose was employed were recognized by the Committee on Medical Resea ch and the U.S.P.H.S (*J 131: 265, 1946*) The failure rate is higher in syphilis of longer duration. Reinfection certainly accounts for some failure but no one knows precisely what proportion. The relapse rate in the 06 cases of ea ly syphilis of Leifer (J 129 1.47 1945) was 8.3% Of 72 patients followed a year o more, 70 were seron gati e; of 60 patie ts whose spinal fluids were ex am ed 6 months o longer afte treatment 60 were normal, including 6 whose fluid were not normal prior to treatment. The investigation of 726 patients deemed to require re treatment aft r pen cillin therapy was interpreted by Thomas and Land (AmJSyph 34 176 1950) to ndicate that at least 50% of the treatment fail res rep esented reinfection. In every retreated pat ent whose spinal fl id was examined, the results were normal.

Th persisting problem of the best dosage and time schedule was el cidated by Eagle t al. (BullJHH 70 169, 1940) who showed that in rabbit syph lis the greater the n mbe of i ject ons the less the total amount of penicillin requ red for cure a d that c re s favorably i fluenced by in reas ng the freque cy and number of injections and the total dose. A total peni llin dose f 000 000 un t wa proved to be inadequate by Sm th et al ADS 55 644 1947) Doses of 600,000 to 1,200 000 its were inadequat too (B nkley et al. ADS 51 200 1945) I adequate doses may temporarily suppress th disease obscuring it and mak ng it clinicall ncosp uous (Magnuson nd Eagle AmJSyph 30 597 1945) so that t trongl adv sable to watch for month a patient who rece ved pe le ll fo gon rrhea nd wa ured of that i fection by a dose nade quat to re syphilis. Precoc ous t rt ar m may follow i deq ate dosage (Marshall: BMJ 61., 104)

The minimum dose in human syph l hould be at least ,400,000 un t in 7.5 days w th terval t ot er 3 hours between i ject ons, said Sehoch and Alexa d (J 130 696 1946) The ,400 000 unit sched le with 3 hou ntervals between doses of 40,000 units yielded satisfactory result i 94 3% of seronegati e primary cases, 89.9% of seropositi primary and 82% of secondary whil post treatment spi al fluid exam a tion f 19 early cases howed abnormality i nly 5 (Sternberg d Leifer J 133 1 1947) Result w th 40,000 units ea h 2 bours for 85 i jectio s and a total of 3 400,000 un t we reco led 25 cases by Arn ld t l (JID 8 280 194) n patient had to interrupt treatment because of rea ti n to the a t bi t c and retreatment wa required for onl 1 of whom 14 showed linical idence of early yphil s wh ch might h e been rei fect n, wh l th rema ng 3 were apparently true stances of serologic relapse or f ilu e. On a queou pe ll n, 200,000 ts ea h 2 h rs fo 3 days, totalling 7,200,000 its, Arn ld t al (JVDI 30 1-3, 1949) la med a e molat v retreatment need of only 5% a d th thought the schedule ffect ve on

Progress contin ng in the development f ffective sched le utilizing prepara tions of slow absorpti n so that treatment can be given to patients of out patie t status,

avoiding the requirement for hospitalization and the 3-hourly needle of the early period of penicillin therapy Case holding o a schedule of 600,000 units twice a week was 93% successful in schedules requiring from 7 to 10 week tried by Scott et al. (JLCM 34: 999 1949) With 600,000 units given twice a week a total dose of 3 000,000 units appeared adequate and advantageously brief to Rausch (NYSJM 49: 1068 1949)

While Cohn et al. (AIS 57: 900 1949) were not able to establish a standard treatment schedule they found total doses ranging from 2,000 000 to 5,000 000 units apparently satisfactory and were confident that treatment with penicillin accompanied by absorption retarding agents would become standard. A schedule of 300,000 units daily for 16 doses was highly effective in primary infections b t somewhat less so in secondary ones reported Chargin et al (ADS 59: 695, 1949) Army experie e reported n by Altshuler et al. (AmJSyph 33 1?6 1949) in 31,000 cases of early syphilis treated with 60 doses of 40,000 units of aqueous penicillin for 7.5 days showed, among 5,600 patient whose CSF wa examined, abnormality in only 0 4%, suggesti g that penicillin prevent or cures early neurosyphilis. Thoma et al. (VDI 28 19 1947) found that th re was no advant ge of injections of penicillin in oil daily over 1 that failure statistics were no worse than with a y other type of rapid treatment and that as with other treatment schedules, most rel pses or r infectio s occurred during the first 6 months after treatment. In their series of 802 patient given 600 000 units daily one group in 2 doses of 300 000 units each and the other 600,000 unit in on dose for 8 days o ly 2 pati nts had to discontinue therapy i both instances because of severe urticaria. A schedule of 8 injections of 300,000 units given in 8 da s appeared satisfact ry in 58 of 60 patie ts treated by Romansky and Rein (J 132: 84 1946) Daily injections of 600,000 unit in wax and oil to a total of 4 800,000 u its was followed by a relapse or reinfection rate of 31% in the e perience of Rauschkolb et al. (ADS 60: 0?0 1949)

An injection once a week of 300 000 units, using a preparation of microcrystalline penicillin in peanut oil with 2% aluminum monostearate to delay absorption, gave theoretically effective blood lev ls for 4 days, this dose given weekly for 4 weeks netted cli ical cures of early cases in 94 % while clinical a d serologic cures amou ted to 89.3%, reported Buschemeyer et al. (AmJSyph 3? 67, 1951) The same preparation given in a dose of 600,000 units daily for 3 days was believed to be an effective regime by Wright et al. (JVDI 31: 225, 1950) Procaine penicillin G i oil with % aluminum monostearate i doses of 600 000 units given twice a week constituted as good treatment as had been devised (Thoma AmJPubH 39: 1361 1949) and on such a schedule the total dose should reach in late symptomatic and eurosyphili tic cases, at least 6,000,000 units given in not less than 15 days.

Penicillin in oil, 300,000 units twice a week for 8 weeks, a total of 4,800,000 units, was considered to be a good treatment schedule by Sobel et al. (JID 15: 18, 1950) In 70 cases given 600,000 units twice week for 8 weeks, total of 9,600,000 unit the cumulative failure rate was 11.3% (Shaffer and Courville: ADS 60 253 1949)

A single dose of 1,200,000 units w s as ffective a a single dose of 400,000 units (Thomas et al.: AmJSyph 35: 473 1951) A single dose of 2,400,000 units cured 0% of dark-field positive early cases (Rodriguez AmJSyph 35 46 1951) Various schedules of giving 1,200,000 units pe dose weekly fo a f w doses all yielded good results for Thomas et al. (AmJSyph 33 523, 1949) A single injection of 1,200,000 units of procaine penicillin was not lequate treatment but such dosage given weekly for from ? to 4 weeks seemed to be as good s any treatment (Jo es and Heyman AmJSyph 36: 250 1952) There seemed to be o significant difference between the results obta ned with 2,400,000 units and with 4,800,000 units of crystall ne penicillin G when these doses were given in a period of 7.5 days (Platke et al.: AmJSyph 35 40 1951); and the cumulative fail re rate of either schedule was about 14% at the end f 1 to 15 months. PAM totaling 4.8 million units, gi en 2.4 the first dose f llowed by 1.2 given twice, constitutes good treatment for primary nd secondary cases, according t Cutler et al. (AD 71 239 1955)

Early syph lis may be cu ed by a single dose and it is incorrect nowadays to wait for indubitable diagnosis, believed Schoch (ADS 65 14, 1952) who n ted that the treatment of early syph lis is bette than statist cs indicate because of the effect of reinfection on statistics. Treatment f reinfect on is at least a successful as treatment of the n tial, early syph litic fect o (Schoch and Alexander ADS 60 090 1949) A single injection of 1.2 mill on un t of PAM often suffices in primary syphilis, and 2.4 million in secondary bel e ed Thomas et l. (AmJSyph 37 574 1953)

Decision as to a dosage schedule has got to be made when one has a patient to treat, and one may recommend a program of injecting 600 000 units in oil with 2% aluminum monostearate thrice a week for 3 weeks (total 5 400,000 units) in cases other than neurosyphilis, in which one may give the same weekly dose for twice as many weeks. One may be fairly confident that a patient treated thus has received about all that penicillin therapy holds for him. If a satisfactory result has not been attained, fever therapy may be indicated unless the unsatisfactory result may be presumed to signify reinfection, which for therapeutic purposes, means simply starting over

The ill effects of penicillin are dermatitis medicamentosa (q v) and Herxheimer reactions, but rarely is intolerance actually a serious menace to the

patient (Thomas et al. JID 10 77 1948) When penicillin cannot be used, one may recall that arsenicals particularly Mapharsen, cured high proportions of the cases treated with them before antibiotics were discovered. The use of tetracycline should be considered.

PENICILLIN COMBINED WITH OTHER THERAPEUTIC AGENTS.—The combination of penicillin with other chemicals may or may not be advantageous, and optimum therapy for human beings has not as yet been determined. It might consist of some combination of penicillin Mapharsen and bismuth (Eagle et al. VDI 27 3 1946) Hyperpyrexia along with arsenicals and bismuth was thought to increase the therapeutic efficacy by Eagle et al. (AmJSyph 31 239 1947) Penicillin plus neoarsphenamine and bismuth seemed better than penicillin alone to Jones (OhioSMJ 47 131 1951) Daily injections of 300,000 units in oil combined with 20 doses of arsenical and 5 of bismuth comprised the ambulatory scheme which was effective in the experience of Hazel (VDI 28 103 1947) Early syphilis treated with penicillin, Mapharsen and bismuth did no better than when penicillin was used alone (Chargin et al ADS 63 104 1951) but the rate of relapse or reinfection was less on combined therapy The prolongation of treatment by combining a course of bismuth injections with a course of penicillin seemed advantageous to Pardo-Castello and Pardo (ADS 61 196 1950) Combination chemotherapy was reviewed by Kolmer (UCutRev 53 338 1949) who could not reach a decision regarding superiority of merits of any particular scheme. The trend at present is to rely on penicillin alone

ARSENICALS, BISMUTH MERCURY AND IODIDES.—The historical aspect of the succeeding paragraphs justifies their inclusion, and the discussion of Mapharsen is significant because the drug is an effectual one in cases where because of intolerance penicillin cannot be given Tests of therapeutic effects in vitro of various arsenical and bismuth preparations were interpreted by Eagle (AmJSyph 23 310 1939) as suggesting a spirocheticidal action

ARSENICALS.—Ehrlich's salvarsan, o arsphenamine the 606th preparation of a series of synthesized compounds, is dioxy-diamino-arsenobenzene dihydrochloride. It is a yellow powder containing 31% of arsenic, soluble in water forming a strongly acidic solution. The average practical dose of arsphenamine for an adult was 0 40 Gm. (6 grains) and the drug was given, *after neutralization* intravenously When ingested, it is poisonous. Exposure to the atmosphere results in oxidation deterioration, and the formation of toxic substances.

Various arsenicals are given intramuscularly subcutaneously or intravenously Acetarsone is given by mouth Neoarsphenamine may be given to infants intramuscularly and sulfarsphenamine was so given to adults. The subcutaneous route is likely to cause slough. The usual route is intravenous.

MAPHARSEN the arsenoxide responsible for the activity of the arsphenamines, superseded old arsphenamine and the later variations (Tatum and Cooper JPharmExpTh 50 198 1934) It was used in many thousands of doses as the standard therapeutic agent in the military services of the U S. A. in World War II, with notably few serious reactions. Its chemistry and effect venesection have been reported on by Cole and Palmer (ADS 36 561 193) R in a d Wise (J 113 1946, 1939) Chargin et al. (ADS 40 *03 1939) Stokes and Beerman (AmJMedSci 201 601 1941) Long (ADS 47 226, 1943) Gay (b p. -35) and many others.

Many other arsenicals have been synthesized and studied (Eagle et al. JPhExpT 69 84 70 11 221 1940)

Toxicity—To treat syphilis wisely toxicology must constantly be kept in mind. See Dermatitis medicamentosa (p. 172)

In investigations of toxicity use is made of the terms *maximum tolerated dose* (M.T D) *minimum effective dose minimum curative dose therapeutic index* (M.T.D. divided by M.E D), and *curative index* (M.T D divided by M.C.D) Grohmt (ADS 32: 848, 1935) stated that T I. of Mapharsen is 18, of arsphenamine is 14 of neoarsphenamine is 9 C.I. respectively is D 11.6 and 8.8 Cole (J 107 1-3, 1936) gave the therapeutic index for arsphenamine as *0 1 to 30 1 bismuth intramuscularly 50 1 and mercury 1:1 to 1 –

Technique of Administration of Arsenicals—ARSPHENAMINE.—All apparatus and solutions must be sterile. Freshly distilled, dependably pure water should be employed. Gravity infusion is safer than injection by syringe. The ampule is tested by immersion in alcohol If intact, its content is sprinkled int a known quantity of water which contains a drop of phenolphthalein, and 0.85 cc normal sodium hydroxide per 0.1 Gm. arsphenamine is added Dilution is made up with water to 25 cc. per 0.1 Gm of arsphenamine The solution, filtered, must be clear and alkaline (pink) It is injected slowly into the vein, at the rate of 0.1 Gm arsphenamine per minute, with great care not to infiltrate outside the vessel. This information is of historic interest only

Inunction has been a valuable method of administration (Sollmann et al. ADS 31: 18 331 1 24., 1935) The 33% unguentum hydrargyri mitis was the favorite preparation, 4 to 6 Gm. daily to be rubbed and massaged into nonhairy regions in turn, so that each area was used only once in 6 days, so that irritation was not likely to ensue. Inunctions were given in courses, a series of daily treatments extending over a period of from a fortnight to a month being alternated with similar periods during which some other form of antisyphilitic therapy might be administered. A series of 40 rubs was often prescribed.

Injection supplied a convenient and efficient method of dosage. Soluble or insoluble preparations might be employed. The injections were commonly made in the gluteal region. Colloidal mercury sulfide was recommended by Zakon and Jacobson (JIDLJ 76: 172, 1939).

Soluble salts were well thought of but to maintain an adequate concentration of the ion, they had to be given at frequent intervals. The bichloride in doses of from 1/12 to 1/8 grain, the succinimide in doses of from 1/6 to 1/4 grain, or the biniodide or benzoate from 1/10 to 1/4 grain might be given once daily or on alternate days. Mercuric salicylate, insoluble and suspended in vegetable oil, was extensively used. The initial dose was 0.065 Gm., and injections were given at intervals of 3 or 4 days.

Heat in the Treatment of Syphilis.—The remarkable effectiveness of penicillin in neurosyphilis has rendered fever therapy almost obsolete. Fever therapy was at one time believed to be indicated in all cases of neurosyphilis unless contraindicated by the patient's estimated inability to withstand it. Until penicillin therapy of meningovascular syphilis had been evaluated—and penicillin alone early proved to be adequate in at least some cases (Gammon et al. J 128 653 1945 O'Leary et al J 130 698 1946 Stokes et al J 131 1 1946 Moore and Mohr *AmJSyph 30 405 1946* Heyman *AmJMedSci 213* 661 1947 Leavitt ADS 56 233 1947)—one could say that neurosyphilis had not been treated adequately until fever as well as chemotherapy had been utilized. See Neurosyphilis, treatment fever therapy

Chemotherapy Combined with Fever.—In primary and secondary infections, the use of fever combined with chemotherapy was considered experimental (Kendell et al APhysM 26 76 1945) The combination of fever therapy with chemotherapy has seemed to be advantageous however apparently yielding better results than chemotherapy alone in early stages of syphilis as well as in late (Heckh and Barnett AIntM 63 974 1939) Fever used to be used almost routinely in neurosyphilis (q v) where various combinations with chemotherapy have been evaluated. Adequate treatment with arsenicals and bismuth has been assessed as yielding when used auxiliary to fever at least twice the spinal fluid reversal rate of fever alone (O'Leary et al J 115 677 1940) See Thomas and Wexler (J 126 540 1944) Epstein (ADS 37 254 1938) *fever adjunctive and helpful especially in CNS syphilis.*

Combinations of penicillin with fever therapy seemed especially promising to Curtis et al (AmJSyph 31 618 1947) and to Schwemlein et al. (J 137 1209 1948) Malaria combined with penicillin was commended by Lescher and Richards (BMJ 2 565 1947) and by Reynolds (AnnIntM 26 393 1947) The cure rate in early syphilis was better with penicillin plus fever than with penicillin alone, reported Plotke et al. (AmJSyph 34 161, 1950) Yet the combination of Mapharsen bismuth, penicillin and fever appeared to possess no advantage over repository penicillin alone according to O'Brien et al. (AmJSyph 36 451 1952) and their view is generally held at this time

Obsolete standard practice utilized more than one agent in syphilotherapy wherein treatment plans involving arsenicals and bismuth penicillin and arsenic and bismuth or fever with these were then modern science while the exhibition of mercurials and iodides in conjunction with these might have been classed as art. Multiple attack upon the infection was empirically known to be effective *the agents used being divisible into the spirocheticides and the* resistance builders. Fever therapy could be called the final resort in difficult cases exemplified by neurosyphilis, resistant syphilis, interstitial keratitis and optic atrophy However when it is correct to use fever therapy at all it is usually correct or even urgent, to use it promptly rather than hesitantly and belatedly after irremediable damage has been done. In the most difficult imaginable case of syphilis, with reservations regarding cardiovascular or hepatic damage disastrous to the victim, the patient could have been said to *have received everything when he received adequate penicillin, arsenical, bismuth* and fever therapy

Nowadays it is felt that, when all detectable debilitating adjunctive conditions have received the attention they deserve and when fully adequate

penicillin therapy has been given, there is reached a time when one can do no more nothing is gained by flailing a dead horse

Nonstandard Chemotherapeutic Agents.—Iodides have been dropped from syphilotherapy completely outmoded. Tryparsamide has been discarded, a dangerous drug of perhaps tonic but no antisyphilitic value. Experiments have been performed with a wide assortment of metals, including magnesium, beryllium zirconium ruthenium, yttrium and others, by Jahnel (ZtschrImmun&ExperTher 91 3L., 1937; 93: 86, 1938; 93: 184, 1938) and no useful agent was found. Rhodium salts apparently cured rabbit syphilis (Pavanati: abs AIntM 64: 1084, 1939) and a vanadium salt seemed effective and low in toxicity (Pereira: abs J 114 933, 1940)

ANTIBIOTICS.—Penicillin is recognized as the best, but next best is tetracycline and then Erythromycin, Aureomycin, Terramycin, Chloromycetin and streptomycin, in that order according to Turner and Schaeffer (AmJSyph 38 81 1954)

CHLOROMYCETIN though it shows no treponemicidal effects in vitro, heals the primary and secondary lesions, and organisms disappear (Robinson et al.: AmJSyph 33 509, 1949) Romansky et al. (Sci 110: 639 1949) observed similar phenomena and a rapid decline in serologic titer in most cases within a month, but Herxheimer reactions were mild or absent. Their cases followed for 6 months (AmJSyph 35 .34, 1951) showed the effectiveness of the drug the dose of which probably should be 60 mg./kg./day for at least 15 days. Willcox (BMJ 1: 467 1950) thought the drug useful because it also cures gonorrhea and chancroid if they too are present.

AUREOMYCIN was first tried in 2 cases of human syphilitic infections by O'Leary and Kierland (PSMMC 23 574 1948) and was found to possess antispirochetal activity Hellman showed that its effectiveness in animal experiments exceeded that of penicillin against some spirochetes (O Leary OklaSMAJ 4 : 315 1949) In 9 early cases given from 750 to 1500 mg. per day healing was prompt, and only 1 case relapsed during a brief follow up, reported Willcox (BMJ 1 1076 1949) The benefits were considered slow by Wiggall et al. (AmJSyph 33: 416 1949) The initial decline in serologic titer is satisfactory but adequate dosage upsets the gastrointestinal tract almost always, stated Rodriguez et al. (J 141: 51, 1949) The comparison with penicillin indicated the slower effectiveness of Aureomycin and the high incidence of vomiting and other toxic reactions, according to Olansky et al. (AmJSyph 34 436, 1950)

The drug reaches the CSF when given orally and favorably influences CSF abnormalities (O'Leary et al. PSMMC 4 302 1949) It also passes the placental barrier (Kierland et al.: ADS 61: 185 1950) In neurosyphilis early results with Aureomycin equal those obtained with penicillin, according to Kierland and O'Leary (AmJSyph 34: 443, 1950) and its usefulness may be considerable in patients who do not tolerate penicillin. In cases of neurosyphilis followed fo a year more or less the early clinical improvement continued but was greatest in the early period of treatme t; no case of asymptomatic neurosyphilis became symptomatic while unde treatment, and all but one showed moderate to marked improveme t (Kierland and O'Leary: AmJSyph 35: 544 1951)

A reomycin may be assessed at this time as effective, but of u determined long range effectiveness (Rodriguez et al.: ADS 60 59 1932; 63: 433, 1951; Taggart et al.: AmJSyph 36: 174 1952)

TERRAMYCIN appears to be effective, fo under treatment with 60 mg./kg./day lesions heal promptly (Hendricks et al. J 143 4, 1950) While 4 of 5 cases of early syphilis became seron gative 1 relapsed with CSF abnormality (Robinson and Robinson: AmJSyph 35 4 9, 1951) The value of the drug is *sub judice*. Terramycin resistance was observed in 1 of 10 cases of early syphilis treated with the antibiot c by Irgang and Alex a der (AmJSyph 37 4 1953) who noted cure of all kin lesions. Herxheimer reactions occ rred n 2 of their patients.

ERYTHROMYCIN.—Spirochetes in culture media are highly susceptible (Keller and Morto AmJS ph 37 3 9 1953) It was found effective in early syphilis by Alexander and Schoch (AmJSyph 38 107 1954)

BACITRACIN, 5,000 units per kg cured rabbit syphilis i one dose (Eagle and Fleischma PSExpe M 68 415, 1948)

CORTISONE may have a bad effect in syphilis, for infected rabbits given cortisone devel ped soft spo gy lesions rich in mucoid mat rial and i demonstrable pirochetes, and wh the drug w withdrawn there was a rebound phenomenon in which the lesio reached an sual ize (T rner d Holla de BullJHH 87: 503 1950; AmJSyph 38 3 1 1954 Fa rable effect f cortisone were reported by de Graciansky and Gropper (la J I 9 6 1953)

Treatment of Neurosyphilis.—Meningeal syphilis responds satisfactorily to chemotherapy meningovascular syphilis responds less well and parenchymatous neurosyphilis, tabes and general paresis respond relatively poorly from the clinical standpoint Penicillin kills spirochetes but does not cure scars.

The quiescent CSF formula by Dattner's criteria does not guarantee a favorable clinical outcome whether it has been achieved by use of penicillin

alone or of penicillin combined with malaria noted Horne (AmJSyph 33 454, 1949) in reporting 11 paretic patients who underwent rapid progression and deterioration despite therapy

Histologic studies on 4 cases of dementia paralytica treated with penicillin were reported by Smith and deMorais (JMentSci 94 0 1948) In 2 of these, who had improved, inflammatory changes were less intense than in untreated cases but in _ of the juvenile type which had not improved deterioration had progressed despite penicillin and there wa no mitigation of the inflammatory reaction. Autopsies on 7 cases of neurosyphilis following penicillin therapy by Gammon et al. (AmJSyph 34: 22 1950) showed that in flammatory lesion had been dissipated but degenerative changes had not

Penicillin alone improved every type of neurosyphilis followed for from 90 days to 3 years by Stokes et al. (AmJSyph 32: 28 1948) whose results appeared to indicate th value of high dosage and repetition of courses, although subsequent courses f treatment yielded no great additional effects. Most patients showed most improvement in the first 00 days, and there was little tendency to relapse Blood tests often failed to improve while the spinal fluid did. Symptomatic improvement was a good after 3 years with penicillin alone as with malaria, but malaria appeared to do more for tabes dorsalis. Penicillin alone was best in asymptomatic neurosyphilis. At the end of 4 years, the good effects of penicillin alone were sustained (Stokes et al. AmJSyph 32: 521 1948) There was a recognizable increase in the proportion of normal, near normal and markedly improved spinal fluids, and it could be concluded that penicillin wa entitled to the status f first choice in therapy on the scores of safety convenience and effectiveness By the end of 5 years, improvement had been observed in 53% of the cases of paresis and in 80% of the cases of tabes and asymptomatic neurosyphilis (Stokes et al.: AmJSyph 33 537 1949) It had become apparent that retreatment is desirable in relapses and slowly responding patients. Yet in any phase of neurosyphilis there was hope for arrest by penicillin. One might observe however serologic cures without clinical improvement, and vice versa. Optic atrophy might be arrested by penicillin alone and tabetic pains relieved. Doses higher than 6,000,000 unit appeared not superior, a d once daily injections were as effective as those given around the clock. There were still required evaluation of the individual case repeated CSF examinations, and prolonged observa tion of the patient.

In various forms of neurosyphili in 106 patie t , a total of 3,000,000 u its gave no better results than older methods of therapy i the opinion of Rose t l. (AmJSyph 29: 487 1945) 5 of whose 6 cases of optic atrophy were howeve , apparently arrested. Intra thecal penicillin wa at one time tried (R bin and Leitch: JMoMA 43: 100 1946; Goldman: J 141: 431 1949) but this procedure was condemned u necessary and dangerous by Dattner et al. (J 141: 1960 1949) Intramuscular injection relieved the shooting pains of tabes in 17 of 4 patient of Koteen et al. (AmJSyph 31 1, 1947) but their patie ts with gastric crises were not helped.

In acute syphilitic meningitis, penicillin alone yields excellent immediate results, and no relapse occurred in 10 patients gi en up to 4,000,000 units in from 7 to 11 days by Nelson nd Duncan (BullJHH 75 327 1944) Th dose should be at least 5,000,000 units, and caref l, prolonged follow p is necessary (Pardo and F rmer AmJSyph 32: 587 1948)

Previous treatme t with other methods did not interfere with f vorable response to penicillin reported Barker (JID 10: 169 1948)

The usual CSF responses were observed by Callaway et al. (SouthMJ 43 41_, 1950), in whose 07 cases some 23% showed little or no benefit the cell count and protein fell fast, the gold curve approached normal m re slowly and the Wassermann changed little. No patient with asymptomatic eurosyphilis developed clinical symptoms during or afte treatment. The clinical response was best in pat ents with symptomatic paresis. Dattne et al. (JVDI 32 33, 1951) reported on 438 pat ents with variou types of active neurosyphilis treated with penicillin only: the disease became inactive in 400 of these, and of the 38 therapeutic failures, 31 were retreated. Of the retreated cases, 27 had normal CSF when *last examined. The routine treatme t with preparations of d layed absorption* consisted a 600,000 units given daily for 15 days.

The lack of correlation between serologic responses of the blood and spi al fluid STS was noted by Scully et al. (AmJSyph 32 24 1948) of whose 313 cases of latent asymptomatic e rosyph li less than 10% becam seronegative. From the laboratory standpoint, penicillin induces certainly as good results as any previously used treatment, and of 43 patients who f iled to respond well ft one course of treatment half responded when the course was repeated with a large dose (Datt er AmJSyph 33 571 1949) Treatment failures may represent underdosage.

The spinal flu d response is most rapid during the first yea after penicillin therapy in all kinds of eurosyphilis, found I graham et al. (AmJSyph 34: 568, 1950) and the percentage of normal nd near normal fluids levels off in the third year Response is slowest and least satisfactory in paresis a d taboparesis, while normal CSF was found in highest proportion in tabes dorsalis. CSF relapse occurred after the third fourth year i 5% of the cases, usually in paresis, taboparesis o tabes dorsalis; d increasing the total dose of penicillin did not seem t affect the ultimate result. Th optim l dose approx imates 6,000,000 n ts, and retreatment produces furthe improvement in only from 3 to 5% Of 603 patients, 30 d ed d ring the 7 year observat on period, but syphilis was a contributory ca se of death of only 5 of them.

See Serologic tests, evaluation (p. 437) Treatment favorable response to (p. 433)

PENICILLIN COMBINED WITH OTHER CHEMOTHERAPEUTIC AGENTS AND WITH FEVER THERAPY.—Nothing seemed to be gained by giving Mapharsen and bismuth in addition to penicillin, in asymptomatic neurosyphilis, reported Johnwick (JVDI 31 303 1950)

Dattner (NYSJM 47: 244 1947) compared patients treated with malaria plus chemotherapy and those with penicillin alone: about 85% of both groups obtained satisfactory results. Relapses were highest among those who received less than 5,000,000 units of penicillin. Dattner (AmJSyph 3 : 399, 1948) reported that only 11% of 301 patients treated with penicillin alone required retreatment, and over half of the original failures responded well to retreatment with larger doses of which the maximum was 9 000 000 units.

Penicillin accompanied by malaria was considered to be the best treatment available in dementia paralytica by Reynolds et al. (J 131: 1-55 1946) Concurrent with fever therapy 3,000,000 units of penicillin was judged to be not adequate for late symptomatic neurosyphilis by Rose and Solomon (J 133: 5, 1947) In tabes dorsalis, penicillin alone in doses up to 20 000,000 units yielded symptomatic improvement in "% of the cases, whereas combining malaria with penicillin resulted in 57% achievement of significant symptomatic improvement in the experience of Chesney and Reynolds (ANeurPsych 59 347 1948)

In tabes dorsalis, penicillin alone does about as well as penicillin plus malarial therapy (Packer and Wong AnnIntM 31 96 1949)

Paretics treated with penicillin alone did as well as those treated with both penicillin and malaria, according to Wong and Packer (AmJSyph 32: "12, 1948)

Artificial fever with hot blankets combined with penicillin gave good results for Epstein and Key (ADS 60: 543 1949) although the CSF Wassermann reversed in only 14.5% of the cases within the first year As judged by effects on CSF complement fixation tests the results of penicillin therapy were not inferior to those obtained with malaria and penicillin (Wong and Packer: AmJSyph 33 535, 1949)

In severe parenchymatous disease, the addition of fever was favored, while in milder cases penicillin alone appeared to be adequate to Kierland et al. (AmJSyph 32: 470, 1948) In 294 patients with late symptomatic neurosyphilis, the comparison of results obtained with penicillin alone and with penicillin plus fever therapy showed that the combination of penicillin with malaria gave better results for Kopp et al. (AmJSyph 32 509 1948) Curtis and Horne (MichSMSJ 47 1111 1948) felt that a final conclusion could not be reached as yet. Response may be faster when malaria is combined with penicillin, even if the end results turn out to be equivalent concluded Curtis et al. (AmJSyph 32 546, 1948) but the 3-year results were equal, they reported later (AmJSyph 33: 5.7 1949) Their 5-year results, with evaluation of 430 patients, indicated that penicillin alone is adequate in all types of neurosyphilis except perhaps severe paresis and optic atrophy (AmJSyph 34 554, 1950) Malaria in addition to penicillin appeared to offer no advantage in the experience of Spiller and Stewart (JID 14: L.1, 1950) a view concurred with by Hahn (AmJSyph 35: 433, 1951) Perlo et al. (AmJSyph 35 659 1951) and Epstein and Allen (ADS 63 419 1951) who would reserve fever therapy as an additive measure only in dementia paralytica, primary optic atrophy tabes dorsalis and cases of penicillin failure. Penicillin with malaria was adjudged the best treatment by Brown (ANeurPsych 66 464 1951) in a study of 50 cases of severe dementia paralytica.

Penicillin may continuously accompany fever therapy malarial or artificial, in doses of from 40,000 to 100,000 each 3 hours or 600,000 units daily of a repository preparation. A course of therapy I consider adequate in any variety of neurosyphilis but superseded by doubt as to the real need of treatment other than penicillin requires 3 weeks of hospitalization, with artificial fever therapy holding the rectal temperature at 105 F for 4 hours on alternate days 3 times a week to a total of 9 bouts and penicillin to a total dose of L,000 000 units. A course of 10 to "0 injections of 0.- Gm. bismuth at weekly intervals might follow th I am confident that a patient who completes such a schedule is not undertreated, and I have not experienced trouble with it administration. Three artificial fever treatments a week are tolerated by patients who tolerate fever treatment at all. During such a hospitalization, I concurrently eliminate focal infection.

Fever therapy with malaria the means most prevalently used and, all things considered, productive of the most satisfactory results, has been effective in all forms of neurosyphilis. It is necessary to supplement malaria with spirochetlcidal antibiotic therapy

MALARIAL THERAPY.—See review of Simpson et al. (BJVD 17 1 1941) Wagner von Jauregg (185) noted its beneficial effects and began using inoculation systematically in the treatment of general paresis in 1917 The effects of malarial therapy may be attributed to activation of the reticuloendothelial system, promotion of the development of the immune reaction, and enhancement of tissue immunity (Brnetsch JIndianaSMA 4- .11 1940)

To inoculate malaria, 5 cc of blood of a malarial patient is injected intravenously without cross matching, and 10 chills more or less, are allowed to follow. If the patient tolerates the infection Quinine or quinacrine is then given in order to kill the plasmodia and stop the chills.

Malaria yields best results when given early in the course of neurosyphilis. In asymptomatic neurosyphilis it was assessed the best agent known, for it prevented half the cases from becoming symptomatic, and it succeeded sometimes after chemotherapeutic agents failed (O'Leary J 110 42, 1938). It fails in paresis due to prenatal syphilis. The best outlook is in patients with acute nervous system involvement who have a background of treatment, but improvement or failure does not parallel the spinal fluid complement fixation reaction (Wile and Hand: AmJSyph 20: 630 1936).

Complications of malarial therapy include (1) fatality from cardiac or hepatic failure or from rupture of the spleen, and (2) nonfatal difficulties, such as headache, vomiting, diarrhea, toxic psychosis, edema, jaundice, purpura, herpes etc. (Head et al. AnnIntM 24: 444 1946 Beberius and Cara (1): AmJSyph 30 320, 1946).

It is possible that a quartan strain may be preferable; it more frequently "takes" than tertian and is a milder disease although the incubation period and duration of infection are longer and more hospital time is consumed (Kroll AmJSyph 24 148, 1940). Chills may be regularized by single doses of Thio-bismol (Cole et al. J 115 432, 1940) although this is seldom necessary or desirable after one has become intimate with the supervision of therapeutic malaria, details of which are not given here. Deaths following malarial therapy were carefully investigated by Wile and Mundt (AmJSyph 26: 181 1942).

Benign tertian malaria (Plasmodium vivax) is generally used, but for persons immune to that, quartan malaria will usually take, among Negroes, Orientals, and people who live in malarious districts. Caution is desirable and it is better to terminate malaria unnecessarily in a number of cases than it is to lose one patient unnecessarily. Headache, malaise, and anorexia with nausea and vomiting are common features of induced malaria. Lightning pains of tabes and psychotic symptoms of paresis are frequently exaggerated during the fever but generally can be controlled by analgesics and sedatives. Exhaustion and prostration which result from loss of chlorides through sweating can be avoided by the routine administration of 1 to 8 Gm. sodium chloride daily. Malaria causes a rapidly progressive anemia. Hemoglobin determination should be performed at intervals, but interruption of the fever need not be considered unless the hemoglobin falls below approximately 7.0 Gm. % or the red blood cells below 2.0 million. In approximately one-half of malaria cases, mild jaundice occurs, perhaps from rapid destruction of red blood cells. Rarely, deep jaundice develops, usually in association with a large, tender liver; when it occurs it should be viewed with alarm. The spleen is enlarged in the majority of cases and is frequently painful. Rupture of the spleen followed by death is a remote possibility but occurs in somewhat less than one in thousand cases. A moderate increase in N.P.N. with albuminuria is frequent and of no special importance. However, renal failure needs always to be considered and especially watched for in elderly patients. Retention of urine is common in tabetic and taboparetic patients and may require catheterization. The blood pressure falls in every case. A reliable sign of the state of the vascular system is the pulse rate, which normally rises to 120-140 during the paroxysms but should fall promptly to 70-90 with defervescence. A persistently elevated pulse rate, 140-160 during fever, 110-130 during afebrile periods, is to be considered a serious sign and calls for termination of the malaria. The diet may be as desired, and every effort should be made to keep the fluid intake at a level of from 3 000 to 4 000 cc per day.

Authorities differ on the amount of fever which constitutes an adequate course of malaria. Some carefully calculate the number of hours of fever above 102° F and try to attain a minimum of 130 hours. Others base the calculations on the number of paroxysms of fever reaching 102 F and above and try to attain a total of from 8 to 12 paroxysms. Either method is satisfactory.

Quartan malaria is less satisfactory than tertian because of the long incubation period of about 3 weeks, the length of time required to obtain an adequate course with paroxysms every third or fourth day and the poor quality of fever which generally occurs. The results of treatment by quartan malaria are, however, good, and the time factor should not deter its use when needed. In individuals found immune to tertian malaria, quartan is the treatment of choice.

The contraindications for malaria are age of 60 years or more unless exceedingly well preserved; cardiac disease with history of congestive failure; hypertension with evidence of renal involvement; extensive renal disease, etc., or extensive healed pulmonary tuberculosis; thrombophlebitis; cellulitis and other potentially severe suppurative infections and physical debility and malnutrition. Malaria carries with it more than ordinary risk in patients with heart disease with aortic regurgitation, convulsions, severe or uncontrolled diabetes, cirrhosis and other diseases of the liver, severe psychotic condition requiring sedation and tabetic bladder with urinary retention.

Malaria should be interrupted for persistent tachycardia (120-140) in afebrile periods; intractable nausea and vomiting; rise in N.P.N. to 70 to 80 mg. per 100 cc; severe prostration and debility; severe jaundice; vascular collapse with systolic blood pressure below 70 mm. Hg, cyanosis, weak, thready pulse and clouded consciousness, convulsions not controlled by medication; severe anemia (below 7 Gm % hemoglobin or below 2 million red blood cells) and detection of infection with falciparum parasites.

See Paul O'Leary (PMDIC 9 750, 1934) best agent in asymptomatic neurosyphilis; Dattner (Moderne Therapie der Neurosyphilis) Wien, 1933; Wile and Hand (AmJSyph 20 570 1936), 10 years experience no help in juvenile paresis; Gelsen (DW kn 104 815 848, 876, 611 623, 1938) statistics of 1,255 patients with 16 deaths, malaria and neoarsphenamine best prophylaxis against tabes and paresis. Kahon (ADS 48 82, 1943) priority of discovery of value of fever therapy belongs to Rosenblum, who used relapsing fever therapeutically in paretics in 1876 (see Lilit J 124 1061 1944); Lilit (J 131 404, 1946) complications of malarial therapy.

Hyperpyrexia May Be Produced Artificially by foreign proteins such as intravenous typhoid injection (Dri... and Shaw J 101: 2016 1933; Nelson OklaSMAJ 27 87 1934; Lawrence AmJSyph 23 789 1944; Smith et al. SouthMJ 38 194 1945; Bellach ConnSMJ 12 848, 1048; Nooj... et al. AmJSyph 34: 153, 1950).

Foreign protein therapy may favorably influence the course of syphilis as an accessory measure especially in resistant cases and in interstitial keratitis. The effect is at least in part due to fever. Since resistance to penicillin therapy is practically nonexistent and since cortisone topically has been found marvelously effective in interstitial keratitis, foreign protein therapy of syphilis is now practically a dead letter. A pyrogenic polysaccharide, Piromen, was thought preferable to typhoid vaccine by Klein and Kulwin (ADS 6_ 571 1950).

Typhoid Vaccine Intravenously in graduated doses may be used for the production of therapeutic fever. The most practical and the safest method is the dilution of stock vaccine in small amounts of normal saline so that 1 cc of solution is equivalent to about 100

million bacilli. For the first treatment a dose of 50 to 75 million is used, for the second treatment 100 to 150 million, and with each subsequent treatment an increment of 100 to 200 million organisms. The temperature response is facilitated by the application of hot water bottles and blankets. If a second injection, one-third to one-half the dose of the first, is given as the fever rises following the original chill, the height and duration of the fever are increased. The injections must be intravenous.

In patients who have had typhoid fever or recent immunization against typhoid this method is frequently unsatisfactory but, in the majority, good fevers may be obtained. Frequently after the first and second treatments, many patients have a prolonged temperature rise associated with considerable general malaise, muscle pains, anorexia, and vomiting. Subsequent treatments, however, are better tolerated.

A course of fever by typhoid vaccine consists of 16 to 8 paroxysms with rectal temperatures above 103° F. Results of this type of fever therapy are inferior to malaria and artificial fever.

Artificial Induction of Fever can be accomplished in several ways. There remains some difference of opinion in regard to the relative worth of artificial fever and malaria, but no doubt exists that in experienced hands artificial fever is comparatively safe and effective in the treatment of neurosyphilis. It has the advantage of being controlled as to elevation and duration. The general physical condition of the patient is improved almost at once. The equipment is expensive, and specially trained nurses and doctors are required for constant attendance during, and for several hours after stopping, the treatment. The dangers are burns, heat prostration or heat shock, and death from cardiac or respiratory failure. Adequately trained, cautious workers are able to recognize signals of danger and are prepared to meet them. It is customary with each treatment to prolong the fever at a level of about 105.6° F. for 2½ to 5 hours. A temperature of 106.5° F. should never be exceeded. Best results have been obtained by a total of 10 to 16 treatments given twice a week. This type of fever cannot be used in all persons. Some patients, although cooperative, unafraid, and anxious to receive treatment, are unable to withstand the heat. As the rectal temperature rises they become increasingly restless, agitated, mentally confused, and uncontrollable by safe amounts of sedation.

Hot baths, electric blankets, radiant heat, air-conditioned cabinets and high-frequency radio devices have been used for therapeutic hyperpyrexia.

Dosage in Fever Therapy.—In any method, a temperature approximating 105° F. rectally maintained for 4 hours is to be attained. This may be repeated on alternate days or twice a week for 10 treatments. The means for obtaining it are not important of themselves and artificial fever is probably as effective as malaria (Simpson et al. VDI suppl. 16 194..). The costs are less, the convenience and control greater, the hazards in expert hand fewer (Simpson et al. BJVD 1 1, 1941). The infrared cabinet is safest. Administration of therapeutic pyrexia demands the undivided attention of an experienced physician and a skilled nurse as well as adequate apparatus.

Artificial hyperpyrexia is well tolerated by patients with normal hearts, kidneys and blood vessels and is contraindicated by age over 60 years, cardiac or renal insufficiency, advanced arteriosclerosis, pulmonary tuberculosis, and late neglected dementia of neurosyphilis.

Complications of heat therapy include burns and vesicles; nausea and vomiting usually commencing toward the end of a treatment, controlled by oxygen inhalation and by intravenous injection of 1,000 cc. of 10% glucose; herpes labialis; tetany due to acidosis and hyperventilation, controlled by calcium gluconate intravenously or by carbon dioxide inhalations. An occasional patient put into the hot box rises in temperature abruptly, extremely, and perhaps with fatal outcome despite things done toward his rescue. Such a possibility can be prevented only by the utmost diligence in supervising the treatment, for if the temperature shoots up, the emergency must be recognized at once. Salt loss, too, is a danger: a gram 3 times a day should be given throughout the course of fever therapy in all cases.

Fever alone will render the dark field negative in 94% of primary lesions and produce recessions of secondary eruptions but it will not alter the positive blood test. Fever alone is inadequate (Simpson et al. AnnIntM 04, 1938).

Good results were obtained by artificial fever in all forms of neurosyphilis but the most satisfactory results were obtained in late meningovascular syphilis and tabes dorsalis. Artificial fever had the advantage over malaria of causing less debility during treatment. In patients with general paresis, the relapse rate was higher among those treated with artificial fever than among those treated with malaria.

See Council on PT (J 103 1308 1934); Simpson (J 103 313, 1938); Kettering hypertherm, Krusen (J 104 123 1935); diathermy, Epstein and Cohen (J 104 882, 1935); infrared cabinet, Bishop et al. (J 101 916, 1933); infrared safest, Popp (PrMDiC 10 200, 1933); complications, Nymann et al. (J 10 194, 1936); in early syphilis, Simpson and Kendall (AmJSyph 21 430 193); in early syphilis, O'Leary (J 110 42, 1938); review and bibliography, Kendall et al. (APh) Ther 20 614 1939); in neurosyphilis, Simpson et al. (VDI 23 4 1 408 411 1942); chemotherapy with fever, Pratt and Ebaugh (J 116 4 4, 1941); in dementia paralytica, artificial fever preferred to malaria, Hirsch and Gessner (VDI 23 320, 1942); keratitis complicating, Kendall (Fever Therapy, Thomas, Springfield, Ill 1951 101 pp) monograph.

Results to Be Expected From Fever Therapy.—*Asymptomatic Neurosyphilis, Early or Late.*—Excellent improvement is expected in terms of prevention of development of clinical forms of neurosyphilis. Especially in patients with group III fluids, some degree of positivity of the complement fixation reaction may persist for many years, even after fever therapy. Other spinal fluid abnormalities should disappear.

Acute Syphilitic Meningitis.—Results are usually clinically excellent, though some cranial nerve lesions such as extraocular muscle palsies and deafness may persist. In adequately treated cases the spinal fluid usually becomes normal, though in some with group III fluids changes may persist in the complement fixation test.

Diffuse Meningovascular and Vascular Neurosyphilis.—Results are variable, depending on the type of lesion. In general, most patients do surprisingly well both from clinical and laboratory standpoints. The spinal fluid STS after showi g some improv me t may remain positive for a lo g time. Ri ing cell count and protein content are forerunners of relapse. In assessi g the remission of clinical symptom in diffuse me ingovascular neurosyphilis, the physician mu t keep in mind neurological residuals which are prone to result from vascular occl sions cortical scar formations, etc. The development of epileptic seizures or the persist ce of painful paresthesia does not necessarily indicate advancement or persistence of the i flammatory process.

General Paresis.—From the standpoi t of its serious potentialities, both in regard to life expectancy an l to residual permanent nerve tissue damage thi form of syphilis constitutes a medical emergency. Years of experience have clearly demonstrated that fever is the form of therapy which can be relied on to arrest the progress of general paresis in the largest percentage of cases. The ultimate success of therapy is directly related to the duration of symptoms prior to the instit tion of adequat treatment. The disease p-pears to be arrested, with return to excellent functional condition in about one-third of patients treated. Varying degrees of incomplete remission with some degree of residual defect take place in about 60%. In about 10% ll forms of treatment are unavailing and death i inevitable. Following the terminatio of fever therapy cli ical improvement usually occurs reaching it maximum at about 6 months. Some cases respo d promptly; in a few cli ical improvement may be delayed a year or more. Improvement in spinal fluid cell count and red ction in protein co tent usuall occu within a few months. Other abnormalities, especially the positivity of the Wassermann test may persist for many years. In spite of maintenance of a satisf ctory clinical status, or t least without evidence of advance of the disease process the spinal fluid should be examined regu larly at 6-month intervals. The cell count and total protein are the first tests to reach normal levels and are the most sensitive i dicators of ctivity. Persistent elevation, o the return to abnormal le els, of eithe or both of these tests sually precedes the development of a clinical rel pse and i dicates the desirability of a second course of fever treatment. The spinal fluid complement fixation reaction and colloid l gold test are less sensitive. Their remaining ab ormal does not necessarily indicat impending relapse. A complement fixation test which remains tro gly positive or revert to positive in 0.1 cc. of fluid 18 months to years after treatment is to be considered an indication of pe sistent ctivity regardless of the other tests, and may foreshadow an ltimate relapse. *A second course of fever may be gi en to a patient with such a fluid examination.*

Tabes Dorsalis in whi h symptoms develop within the first 10 years of the disease, or in which symptoms come on acutely shows the strongest spinal fl id reactions. Paradox ically these are often the cases which obta n the greatest benefit from treatment. Conversely patie ts with a long history of visceral rises, light ing pains, and slowly developing ataxia show the least acti e spinal fluids and obtain disappointingly little benefit from antisyphilitic treatment.

Optic Atrophy.—The results of fever therapy depend on the degree of damage before treatment is instit ted. In general, in pat ents in whom visual acuity in the better eye is 20/40 or better there is about an e en chance of rrest of the atrophic process and the maintenance of useful vision.

Treatment of Optic Atrophy.—There is more exigency for fever therapy in this disease than in any other form of neurosyphilis. Malaria should be induced at once wrote Bruetsch (J 130 14, 1946) in all patients with failing vision. Malaria therapy appeared to have no value when visual acuity had diminished below 20/200 stated Blatt (abs AmJSyph 34 390 1950)

Optic atrophy call f at lea t 5,000,000 unit of pe cillin plus from 10 to 1 malari l bouts (W rst r Vrought BMJ 2 659 1947). Pe icillin therapy in 50 cases was followed by progression of isual d fect in 10 patients, 8 of whom became blind (Klander a d Gro AmJSyph 33: 234 1949). Penicilli alone seemed a effective as when combined with malaria in the experience of Horne and Curtis (AmJSyph 33 143, 1949). Penicillin seemed ffecti e in arresting the early st ges, but when vision was worse than 20/50 there ually occurred f rther loss despite the antibiotic, observed Dento and Harris (AOphth 48 449 1952)

Treatment of Tabetic Crises.—The agony may be almost insufferable and its relief a challeng g probl m Si ce th pinal fl d changes re gen rally slight, and ma even be absent, penicillin, capable of reversing CSF evidence of inflammation, seldom c complishes m ch. Fev therapy sometimes increases the pains. The vasodilator drug, Priscol was reported to be usef l (Rogers J 140: 7 1949) Chordotomy was required and was helpf l in a se of Mayne (BMJ 1 1309 1953) ACTH gave relief in a patient f Walner d Mendelsoh (J 152 03 1953) within a few hours.

Congenital (Prenatal) Syphilis

Prenatal Syphilis is a good name for diaplacental infection of the fetus. Infection occurs in utero In this stage it is usually curable

Immunity in the infantile type of disease is as variable as in the adult. Miscarriage stillbirth prematurity and actively syphilitic living babies are

the common results of infection yet normal babies may be born to syphilitic women. Infection in the fetus may be expected to damage structures while they undergo embryologic development. Nevertheless, congenital syphilitics may for many years show no sign of activity of the disease.

Colles (1837) noted that an apparently healthy man might marry and transfer syphilis to his wife without showing any evidence of the disease himself. Colles observed too that a woman without obvious venereal symptoms may bear a syphilitic child and nurse it with impunity even though others are infected by it. Profeta (1865) saw apparently healthy children being nursed by obviously syphilitic mothers without becoming infected. It is generally believed at present that if the child is diseased the mother must be infected, although her disease may be latent.

Spirochetes have never been demonstrated in fetal tissues earlier than the fourth month and rarely before the fifth. At term however the tissues are teeming with them, particularly the liver. The fetus can acquire syphilis from its mother shortly before or at the time of birth. It is generally true as Kassowitz law asserts, that there is progressively less likelihood that the successive children of a syphilitic mother may be infected for with the passage of time the woman's immunity is likely to prevail yet it happens that the disease may skip one pregnancy to damage the next a phenomenon explicable on the assumption of variations in the degree of immunity of the mother.

Showers of spirochetes occur from time to time in any syphilitic person, it is thought. If this happens in a pregnant woman, the fetus will be infected. Since it may happen it must be prevented from happening. Cole et al. (J 106 464 1936) concluded **The data show that congenital syphilis is practically a preventable disease. Its prevention is dependent on the routine, early and repeated use of the serologic blood test on every pregnant woman and on adequate treatment once the diagnosis of syphilis has been made.** Serologic tests should be repeated near term in order to detect syphilis acquired late in pregnancy (Heyman and McCain NEngJM 241 960 1949).

Some 25% of the pregnancies in syphilitic families result in miscarriage *or stillbirths, and fetal death is at least twice as frequent in syphilitic as in* nonsyphilitic families. The earlier in pregnancy that antisyphilitic treatment is given the greater the probability of its success in securing a nonsyphilitic offspring (Soloway J 129 500 1945).

Acquired Syphilis in Infancy and Childhood has *frequently* been observed (Creswell et al. AmJDisChild 66 611 1943). A newborn with a scalp chancre *presumably inoculated* in the birth canal, was [illegible] by Quiroga (abs ADS 42 601, 1940). Sad circumstances of transmission by nonsexual contact *were reported by Murrell and Gray (BMJ* [illegible] 1947). The age range in 35 cases of Waugh (AmJSyph 22 607, 1938) was from 5 months to 14 years. Epidemiology was emphasized in the extensive review by Smith (AmJSyph 23 165 1939). Four sisters [illegible] from 6 to 11 years of age were infected by one youth, reported Schoch and Long (AmJSyph 23 186, 1939). Overcrowding, ignorance and an infected member of the family [illegible] the [illegible] leading to nonsexual infection of 20 little children whose case histories were given by [illegible] et al. (JVDI 30 [illegible] 1949).

Reinfection with acquired syphilis has been described in congenital syphilitics; the *fifth known case* [illegible] *on record by Grimble and Hahn* (AmJSyph 36 439 [illegible]).

Twins.—Congenital syphilis affecting only one of a set of twins has been observed (Wile and Welton AmJSyph 22 544, 1938; Smith and Spence SouthMJ 34 147 1941; James [illegible] 61 359 [illegible]; Rakin AmJSyph 35 334, 1951). The twins may or may not be [illegible] in each case.

Third Generation Syphilis, the transmission of infection from a congenital syphilitic to his offspring possibly may occur although the difficulty of proving that it has occurred is evident (Brassel ADS 40 [illegible], 1939).

Early Symptoms.—Cutaneous Lesions may be present at birth, or may develop during the first 4 or 5 months. Syphilitic babies are generally marantic emaciated and feeble with thin wrinkled skins, and wizened senile faces. Coryzal symptoms often accompanied by rhinitis snuffles, and hoarse breathing may be among the earliest manifestations. Mucous patches and condylomas are likely to be present during the first few months, and these lesions often develop prior to the appearance of the general exanthem. The





Fig. 565.—Prenatal syphilis marasmus, snuffles, fissures radiating from the angles of the mouth. (Cole J 109 580, 1937)

Fig. 566.—Congenital syphilis. (Dr Sam E Sweitzer)



Fig. 567.—Prenatal syphilis etic syphilitic dermatitis nd bullous eruption on palms nd soles. (Cole J 109 580, 1937)



Fig. 568.—Osteitis in prenatal syphilis. Roentgenogram showing defects of ends f radius and ulna in syphilitic infant (Dr Galen Tice, U of Kansas Medical Center)

character of the cutaneous eruption varies. Bullous lesions may occur in hereditary syphilis. The blebs range in diameter from 1 to 5 cm., and are usually only partially distended, with eroded bases and flabby fragile walls. Such lesions may be generally distributed, but often they are limited to the palms and soles. They are likely to be intermixed with macules, maculopapules, and occasionally pustules. Lymph node involvement is often present, but is not a typical or characteristic feature The commonest types of eruption are the papular and maculopapular Fissures of the lips, angles of the mouth, and anus are present in some three-fourths of the cases. Pustular lesions like bullae usually indicate a grave infection. Tubercular and gummatous lesions seldom occur early in the disease See Cole et al. (VDI Supp. 7 1940) Wile and Mundt (AmJSyph 26 70 1942)

The early manifestations of prenatal syphilis (Cole J 109 580 1937) correspond to the secondary stage of acquired syphilis. Ordinarily they show up some weeks after birth. Prenatal syphilis can simulate any of the features of acquired syphilis, excluding cardiovascular manifestations. The child is restless, cries feebly but frequently and has snuffles. A reddish brown or coppery eruption is seen most frequently on the palms, soles, and diaper area It is comparatively easy to find *T pallidum* by dark field examination of material from the perionychium, rhagades, and moist papules or bullae Physical examination reveals a liver enlarged, even perhaps to the level of the umbilicus, and an enlarged spleen

Late Symptoms.—There is a late stage of prenatal syphilis, as of acquired syphilis, in which the disease shows a tendency to localize in certain parts or organs (Smith AmJSyph 24 755 1940) In the Cooperative Group study approximately 33% suffered from parenchymatous or interstitial keratitis 12% had involvement of the central nervous system and 7.2% had involvement of bones and joints.

DISEASE OF THE BONES is found in a fair percentage of the cases consisting of thickening at the end of the long bones, especially the radius and ulna. Owing to pain the child holds the limb as if it were paralyzed (Parrot's pseudoparalysis) X ray examination reveals the characteristic epiphysitis (Black JPed 14 761 1939) from which must be differentiated the lines caused by bismuth therapy given the mother (Whitridge AmJSyph 24 223 1940) Periostitis and occasionally dactylitis are seen. Roentgen findings thought most trustworthy in diagnosis by Black are (1) well-defined saw tooth metaphysis in well-calcified bones (2) multiple separation of epiphyses, with or without impaction in bones which are not rachitic (3) bilaterally symmetric osteomyelitis of the proximal mesial aspects of the tibiae (4) multiple circumscribed osteomyelitis of long bones showing patchy areas of rarefaction (5) multiple longitudinal areas of osteomyelitic rarefaction in the shafts of long bones sometimes resulting in fractures (6) foci of destructive rarefaction at the mesial or lateral aspects of the metaphyses and (7) multiple areas of cortical destruction generally seen within 1 cm. of the ends of the bones.

More osseous lesions are to be found in infants less than 5 months old and are of the form of generalized osteochondritis and periostitis after 1 year osteitis and osteomyelitis are usual and periostitis is seen (Russo and Shryock Radiol 44 477 1945) See Hill et al. (JPediat 30 547 1947)

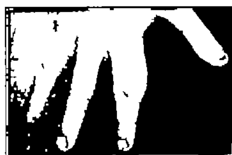
Gross destruction of joints may occur and a rare example of Charcot elbow joint was reported by Denker and Kennedy (J 114 408 1940)

Symmetric, serous synovitis of the knee joints, with hydrarthrosis, is a manifestation seen in congenital syphilis and known as Clutton's joints (Klauder and Robinson J 103 236 1934 Clutton Lancet 1 391 1886)

Syphilitic osteitis and periostitis often affect the sternoclavicular joint the ensuing enlargement being known as Higoumenakis sign (Higoumenakis DZtschrNervenh 114 288 1930 AnnDD 8 939 1937 Dorne and Zakon ADS 32 602 1935) It was present in 30% of 64 congenital syphilitics observed by Dax and Stewart (BMJ 1 771 1939)

Gummas may affect the bony structure anywhere but are found most frequently in the tibia skull bones of the nasopharynx and bones of the upper extremities, especially the inner end of the clavicle Trauma is a factor in their localization. Saddle nose results from destruction of the bones of the nose Gummas may affect soft parts as well as bony structures. Late involve





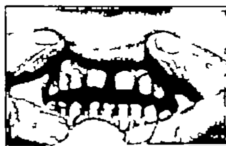


Fig. 569 —Saddle nose, in prenatal syphilis (Dr Jaques P Guequierre.)
Fig. 570 —Syphilitic periostitis of the finger
Fig 571 —Hutchinsonian teeth in a patient with entire Hutchinsonian triad keratitis, deafness, and dental defects. (Dr Grover W Wende.)



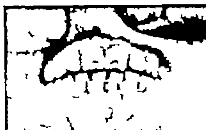




Fig. 572.—Rhagades in congenital syphilis. (Dr Robert Y Andrade.)
Fig 573.—Deformity of teeth, due t syphilis. (Dr D C. Smith.)
Fig. 574 —Hutchinsonian incisors. (Thoma Oral Pathology ed. 3, Mosby 1950.)

ment of the bones occurs most frequently in the form of diffuse osteitis or in a form of chronic hydarthrosis of the joints (Clutton's joints). The knees are most frequently affected (Loos AfDuS 181 549 1940). Osteoperiostitis is a diffuse hyperplastic process most often affecting the tibia. The periosteum is inflamed, and there is thickening from new bone formation leading to the "saber shin" appearance. The enlargement of one sternoclavicular articulation, Higoumenakis' sign, is as significant of the existence of late prenatal syphilis as are other important stigmas (Yang ADS 41 1060 1940).

The Teeth often show deformity (Karnosh ADS 13 25 1926). The variation of dental defects is wide, ranging from a complete failure to develop to a slight diminution of size or alteration of form, and these differences are largely of degree. The characteristic features are the undersized malformed appearance, the contracted appearance of mamelons, marginal ridges and cusps of incisors, cuspids and molars, and a peculiar open bite malocclusion (Anderson AmJDisChild 57 52, 1939).

Dwarfing of the affected teeth and lack of development of the premaxilla were the abnormalities stressed by Johnston et al. (Am. J. Orthodont. 27 667 1941) who could not demonstrate spirochetes in the dental structures. The effects of syphilis on the teeth depend upon the developmental stage during which the disease was active, and roentgenologic diagnosis from studies of unerupted permanent teeth can often be made according to Sarnat et al. (J 116 2745 1941).

The teeth especially affected are the permanent upper central incisors, the lower central and lateral incisors and the first molars (Sarnat and Shaw AmJDisChild 64 771 1942). Dental anomalies occur in approximately half of all heredosyphilitic children. The true Hutchinsonian incisor shows deformity of the developmental lobes of the permanent central incisor and is not due to transitory calcium deficiency. The upper incisors especially are narrowed and somewhat smaller than normal, are bowed out on their sides, and show a central depression of the cutting edge due to hypoplasia of the middle lobe. The true mulberry molar of syphilis is a permanent first molar characterized by enamel cusps showing crests of sound enamel on a base of hypoplastic deposits, the cusps being crowded together on a crown surface of dwarfed dimensions.

The budlike molar of Pflüger (see Kreyberg and Schwisow ZtschrNeurPsych 127 188 1930) was independently described by Karcher (ADS 31 661 1935) and is quite typical; the diameter of the crown is normal but the cusps are rolled in, giving the appearance of being clinched, and there is no defect of enamel.

The recognition of syphilitic dental dysplasias can contribute to public health case finding efforts (Beecher et al. JVDI 32 70 1951).

Ocular Manifestations of some kind develop in about 5% of all syphilitics sometime during their disease according to Woods (AmJSyph 27 133 1943). From birth until age 2 years, optic neuritis, choroiditis and retinitis are not extraordinary and the results may be either progression and atrophy or recovery. Between the ages of 2 and 8 years, interstitial keratitis is the usual ocular finding. After the age of 8 years occur interstitial keratitis, eighth nerve deafness, neurosyphilis and optic atrophy. Ocular examination may reveal diagnostic findings even when the changes are not conspicuous and when other signs of congenital syphilis are absent (Gross and Meyer AmJSyph 38 30 1954).

Interstitial keratitis occurred in a third of 1,010 cases of late prenatal syphilis surveyed by the Cooperative Clinical Group (Cole et al. ADS 35 561 1937). Patients less than 15 years of age did better than older patients, but there was a risk of the development of the disorder up to age 25 years. Adequate treatment strongly diminished the likelihood of its appearance. Interstitial keratitis appeared 5 years after antisyphilitic therapy had reversed the STS to normal in the case of Robinson (AmJSyph 36 92, 1952).

Of 637 patients with interstitial keratitis, 40% had dental stigmata, 35% bone and joint lesions, 10% labyrinthine disease, 8% chorioretinitis, 8% neurosyphilis (Klauder and Vandoren: VDI —: 307 1941) When one eye only was involved, the disease became bilateral within 1 month in 4?% and within 10 years in 9?% of the cases. Interstitial keratitis may appear any time from 4 or 5 years of age to 20 or 25 years. The cornea develops a diffuse ground-glass appearance different from the sharply defined phlyctenules seen in tuberculous keratitis There are extreme photophobia, lacrimation and circumcorneal injection of the ciliary vessels. These vessels may invade the cornea. In severe cases there may be iritic changes in the choroid and peculiar opacities in the vitreous.





Fig. 575.—Saddle nose resulting from prenatal syphilitic osteitis. (Dr Howard Morrow.)
Fig. 576.—Prenatal syphilis gummatous osteitis of the skull. (Dr Grover W Wende.)



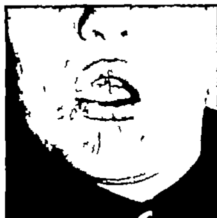


Fig. 577.—Interstitial keratitis early stage of clouding of cornea (Dr C. C Dennie.)
Fig. 578.—Syphilitic rhagades (Dr F Ronchese.)

It is common for the second eye to become involved, especially when therapy has been neglected, and blind eyes the result. Slit lamp examination of the cornea may reveal interstitial keratitis which is asymptomatic (Klauder and Cowan: J 113 1024, 1939)

The exact mechanism whereby syphilis damages the cornea is not known although spirochetes are plentiful in all parts of the eyes of the congenitally syphilitic fetus (Woods: AmJSyph — 133, 1943 Avitaminosis perhaps the lack of riboflavin may be concerned (Kruse et al. PHRpt 55 15 1940) Klauder et al. (AmJSyph 35 416, 1951) considered the endocrine aspect of etiology finding the BMR and the urinary 17 ketosteroid output lower than average in these patients.

Chorioretinitis in congenital syphilis may be classified in 4 types (1) salt and pepper fundus (2) oval pigmented yellowish red lesions occurring singly or in groups (3) light yellow peripheral lesions remaining small or undergoing confluence and (4) lesions simulating primary pigmentary degeneration of the retina and carrying a poor prognosis (Sidler Huguenin, cited by Klauder and Meyer AOphth 49 139 1953) Chorioretinitis is not statistically so important a cause of blindness as interstitial keratitis is.

DEAFNESS is a distressing result of late prenatal syphilis. It may be mild or total. It may come on slowly or at a certain stage progress with great rapidity If it has progressed far it does not respond well to therapy It usually reveals itself from the age of 6 or 8 years to the age of 20 or 25 Hutchinson s syndrome is not always evident in 25% all 3 symptoms—deformities of the eyes, ears and teeth—are noted. Changes in the internal ear and deformities of the teeth are present in about 10% involvement of the eyes and ears in 40% and involvement of the internal ear alone in 25% Histologic studies of the auditory apparatus in congenital syphilis have been given by Mayer and Fraser (JLaryngOtol 51 683 755 1936) and Carnevale (abs VDI 20 83 1939)

THE CENTRAL NERVOUS SYSTEM is commonly involved This seems more frequent in the earlier years of life than later An incidence of from 20 to 40% has been quoted. Syphilitic meningitis gives evidence of pressure symptoms the fontanel is tense acute hydrocephalus may be present and convulsions may occur The spinal fluid shows the usual changes. Paralyses of various types are also seen in these young patients. With parenchymatous involvement of the brain tissue juvenile dementia paralytica is encountered The symptoms may show up at any time from the age of 5 or 6 years to 20 or 25 In cases in which there is involvement of the posterior columns of the cord, the picture of tabes dorsalis presents itself often accompanied by optic atrophy The incidence of neurosyphilis in congenitally syphilitic children is higher among those born to neurosyphilitic parents than among an unselected group suggesting some credibility in the hypothesis of a neurotropic strain of the spirochete reported Quisenberry (HawaiiMJ 9 94 1949)

CARDIOVASCULAR INVOLVEMENT in congenital syphilis is rare, occurring in interstitial and nodular forms. Arteritis but not valvulitis may be caused (Hinrichson AmJSyph 27 319 1943)

Pathology—In the umbilical cord the inflammatory infiltrate is rich in polymorphonuclear leukocytes, which are not a usual feature of syphilitic tissue reaction. Dark-field examination of scrapings from the umbilical cord were positive in over half the cases of Ingraham (J 105 560 1935) The placenta is larger than usual with thickened rather avascular villi. Sometimes it exhibits little positive evidence of disease although the child shows much. Dippel (AmJObGyn 47 369 1944) did not find spirochetes in any fetus younger than 18 weeks in 67 necropsies of syphilitic infants. Spirochetes in large numbers are in the liver spleen, kidneys, adrenals heart muscle bone marrow and testes. Diffuse fibrosis is seen particularly in the lungs pancreas, heart and adrenals. The liver may show areas resembling gummas but infiltrated with enormous numbers of spirochetes. Congenital syphilis probably does not occur in the experimental disease in mice and rabbits (Kemp and Fitzgerald JID 1 353, 1938)

Diagnosis is usually easy when the disease is clinically in evidence Mucous patches and condylomas about the mouth and anus are characteristic features The occurrence of palmar and plantar bullae also is almost pathognomonic The cutaneous lesions are basically similar to those of the secondary eruption in acquired syphilis. Perioral lesions result in atrophic scarring of the elastic tissue and typical scarring rhagades, which are linear depressed pale furrows seen on the lips and extending radially in the perioral skin (Strakosch and Nelson ADS 43 664 1941)

Quantitative STS showing significant increases in titer of reagin in syphilitic infants after 4 to 8 weeks, aid in diagnosis (Ingraham ADS 43 323

1941) Practically 100% of persons with prenatal syphilis have positive serologic reactions. Early treatment is likely to reverse these but the longer the child remains positive and untreated the less likely is therapy to influence the blood test. The cord blood test is not a dependable guide as to the existence of syphilis in the newborn because his serum is likely to react as the mother's does, showing passive reaginemia even though the infant may be nonsyphilitic. Syphilitic reagin in the blood of the newborn is diagnostic of syphilis in the mother not in the child a fact known as Fildes law Such reagin, if the infant is not syphilitic, falls far toward zero even in the first week after birth (Faber and Black AmJDisChild 51 1257 1936) If physical and roentgen examinations of the infant are negative, quantitative tests at intervals of 2 weeks are indicated Persisting high titer or increase of titer for 6 to 8 weeks justifies treatment In the nonsyphilitic infant with positive tests at birth, titer is usually as low as 4 to 8 units within 3 weeks or negative but positivity occasionally persists into the third month. When the test is positive at the age of 8 weeks, there is 90% likelihood of the coexistence of positive x ray changes. It is inadvisable to give antisyphilitic treatment to infants of syphilitic mothers unless the infants are proved to have the infection

LANDMARKS OF TARDIVE HEREDOSYPHILIS (after Stokes)

MAJOR (strongly presumptive or diagnostic):

- Positive blood Wassermann.
- Interstitial keratitis.
- Hutchinsonian incisors.
- Mulberry molars.
- Eighth nerve deafness.
- Epiphysitis and osteochondritis.
- Saber tibiae.
- Osteitis of the nasal septum.
  - Snuffles.
  - Saddle bridge.
- Early dactylitis.
- Splenomegaly before the fourth month.
- Rhagades and scars.
- Roentgenographically specific changes.

SECONDARY (alone insufficient for diagnosis):

- Frontal bosses.
- Aplasia of incisor teeth.
- Scaphoid scapula.
- Marked enlargement inner third of clavicles.
- Disturbance of age-development ratio.
- Precocity and irritability
- Early epitrochlear adenopathy
- High narrow palatine arch.

MINOR

- Venous ectasia.
- Hypertrichosis.
- Ulnar deviation of middle fingers.
- Constitutional subnormality
- Backwardness.
- Hypertrophic frontal suture
- Craniotabes.
- Bilateral dacryocystitis in childhood.

DEBATABLE

- Carabelli tubercle.
- Retromastoid adenitis.
- Persistent infantile hydrocele
- Knock knee elbow
- Absence of the xiphoid process.
- Hypertrophic thymus and thymic abscess.

Roentgenograms are diagnostic in a higher proportion of cases than serologic tests (Evans J 115 197 1940) Roentgenologic diagnosis can be made in 95% of young patients in contrast with 30% diagnosticable by serologic methods, according to Parmelee and Halpern (J 105 503 1935) Within the first 4 months x ray examination discloses, when they exist, osteochondritis, epiphysitis, diaphysitis and periostitis (Holmes and Lingley NEngJM 217 983 1937) The involvement of bones in the fetus may be recognizable even before birth, by x ray examination.

Treatment.—Antenatal treatment of syphilitic women prevents syphilis in babies. Penicillin is the best therapeutic agent. While it is inadvisable to treat an infant for congenital syphilis unless he has been proved to have the disease (Ingraham AmJSyph 19 547 1935) it is highly advantageous to the syphilitic child to receive treatment early in the course of his infection (Smith AmJSyph 19 512, 1935 20 45 1936) and this should be done before the infant is born if possible (Foerster WiscMJ 36 987 1937)

PRENATAL TREATMENT DURING PREGNANCY —The value varies with the relative adequacy of the treatment, and in prepenicillin days it was observed that with increasing dosage of arsenicals and bismuth there was a steady fall in the number of fetal casualties (Dill et al. AmJObGyn 40 965 1940) Adequate therapy with either arsenicals and bismuth or penicillin gave equivalent results approximately 94% normal full term infants and 2% living syphilitic infants in the experience of Wammock et al. (AmJObGyn 59 806, 1950) When at least 2 400 000 units of penicillin had been given to the mother 95% of the babies were nonsyphilitic (Speiser et al. JVDI 28 108 1947) Not one syphilitic offspring appeared among the mothers whose STS became negative under treatment prior to delivery although syphilitic infants were born to 9% of the women who received less than 2,400 000 units of penicillin (Cole et al JVDI 30 95, 1949) Women who received 2,400 000 units or more bore syphilitic infants in only 2.5% of the instances.

Treatment should be begun before the fifth month of pregnancy If early syphilis appears late in pregnancy proper treatment carried through term will increase the likelihood of the birth of a healthy baby To ensure a *living nonsyphilitic infant it is necessary to treat the mother during each* pregnancy thought Peckham (J 117 1863 1941) It is now believed not necessary for a woman who has had syphilis to undergo treatment during every pregnancy provided that she has received 4 0 Gm of Mapharsen or its equivalent or 2 400 000 units of penicillin and provided that she is without signs of active syphilis and has negative STS or STS of 8 units or lower titer wrote Goodwin and Farber (AmJSyph 32 409 1948) Other authorities agree that it is not necessary to treat a pregnant woman for syphilis if she has been cured of the disease and has not been reinfected (Ingraham et al. AmJObGyn 56 340 1949 Tucker AmJSyph 33 1 1949 Goodwin JVDI 31 178 1950 Shaffer and Courville ADS 63 91 1951) The problem, obviously is to decide when the presumed cure is sufficiently secure to let the fetus carry the risk while retreatment with penicillin is not a great hazard to the mother and nowadays penicillin is cheap

Treatment with penicillin is remarkably effective in syphilitic pregnant women and is, in fact so superior for this purpose protecting the child even when started late in pregnancy that it supersedes all other possible choices of therapeutic agent (Aron et al. ADS 58 349 1947) Massive arsenical therapy is ill tolerated by the pregnant woman who is more liable than other syphilitic patients to the hazards of hemorrhagic encephalitis (Speiser et al. AmJObGyn 49 214 1945) *it should never be used* The reaction rate to arsenicals increases as the pregnancy progresses (Kennedy and Henington ADS 48 83 1943) The antisyphilitic superiority of penicillin is conspicuous and *results are equally good no matter what the duration of pregnancy at the time* treatment is commenced, thought Horne and Curtis (MichSMSJ 47 1006 1948) They recommended doses of 600 000 units daily for 10 days, using a preparation of slow absorption rate They stressed the necessity for adequate clinical and serologic follow up of both mother and child A dose of 600 000 units daily for 8 days seemed adequate to Bundesen et al (ADS 62 230 1950) See treatment in pregnancy (p 442) rapid treatment methods (p 449)

The occurrence of Herxheimer reactions was, in 2 instances among 182 cases of serious consequence to the fetus, reported Bowen et al. (ADS 58 735 1948)

GENERAL MEASURES include hygienic and supportive efforts. The nose should be kept clean, the folds of the skin should be free from moisture and dirt, and such mucous patches or condylomas as may develop should receive topical attention though they respond promptly to specific therapy Frequent baths, followed by the liberal application of a bland dusting powder are useful Hospitalization and expert pediatric care are highly desirable for many congenitally syphilitic infants suffer severe anemia dehydration hypoproteinemia and difficulties of salt and water balance.

PENICILLIN was reported effective in a total dose of 18,000 units per pound by Lentz et al. (J 126 408 1944) who at that time believed that the first doses should be cautiously small to avoid serious reactions. It is now known that such a total dose is much too small (70 000 units per pound being perhaps adequate) that caution in the first injection is not necessary that the antici pated cure rate in infants with early syphilis approaches 100% and that no adjunctive chemotherapy is necessary in the early period of treatment. Ex tensive studies of penicillin dosage and effects by Smith et al. (ArchPediat 72 12, 1955) indicated that the total dose should approximate 320 000 units per kilogram body weight 1 2 million to 4 8 million units according to the age of the child

When 0,000 units pe pound are given i 60 doses at 3-hour i tervals seronegativity does not promptly appear but the n mber of patients becoming seronegative increases monthly for at least 18 month (Pl tou et al.: AmJDisChild 7 433 1946) Larger doses continued over a longer period of time result in improvement in results (Ingraham et al.: J 130: 694 1946)

Following treatment the infa t should be examined at monthly intervals with titered serologic test as long a the tests show positi ity Intervals for re evaluation may be lengthened to 3 month aft r seronegativity i attained, a d the spi al fluid must be ex ami ed about 1 year late If infectious relapsing lesion occur at any time after the commencement of treatment or if the serologic test is still strongly positiv afte a year of postre tment observation, retreatment on an i dividualized basis is to be consi lered.

The dose of penicillin recommended by Platou et al. (J 133 10, 1947) on the basis of studies of .3 cases treated with penicillin in 5 university clinics, wa 100 000 units of penicillin sodium per kg body weight divided into 120 equal injections given at intervals of 3 hours in a period of from 12 to 15 days. Results i cluded dramatic clearing of active manifestations of infection, 0 relapses within 11 months, seronegativity i the majority of the patients within 4 to 1 mo the following the py and *7 death from ll causes. Result from a si gle course were satisfactory in 72% of the cases, unsatisf ctory in 9% per cent, and ncertain in 19% When spinal fluid abnormalities were prese t at the out set, they improved remarkably

PRIOR TO PENICILLIN which i the drug f choice because of its effectiveness, safety and col eidental val e gainst the intercurrent i fections debilitated infants usually suffer (QMN: J 131: 1535 1946) it was judged correct to st rt the ch ld who had active pre atal syphilis on arsenical treatment t once giving neoarsphenamine from 0.01 to 0.015 Gm. per kg Intra enous injection in infants require some skill; the fo tanel may be pu ctured to introd ce the med cine int the superio sagittal sinus. The drug was dis solved in cc. of distilled wate Moore at one time preferred sulfarsphenamine, from 0.010 to 0.015 Gm. per kg., administered i tramuscularly into the buttock in a con centrated solution. Ordi narily a course of 8 weekly injections of eithe preparation was employed, immediat ly followed by a series of weekly i tram scula injections into the b ttock of a preparation of bismuth, such as th oil suspension f bismuth salicylate 2 mg./kg (N ef and Vieth SouthMJ 33: 691 1940) Courses of the two drugs might be alternated until a yea of th rapy had been completed bout 25 injections of each preparation (Howard JPed 14: 220 1939) If th serologic reaction was still positive at the end of the yea furthe treatment for 6 month o a year was n orde Mapharsen and bismuth w re preferred by Astrachan and Corn ll (J 121: 746, 1943)

Acetarsone once popular because of the simplicity of its oral administration is a da gerous drug, although it ha cured many pat ents. Its antisyphilitic activity was demonstrated by Pillsbury a d Perlman (AJDC 39: 909 1930) who bserved its ability to reverse serologic test ; but serious reactions occurred in 4.6% of their 87 cases. Lyon and M (JPed 13 13 19 1939) consid red t a good a other arsenicals. The dose schedule of Maxwell d Glase (AmJDisChild 43: 1461 1932) consisted of 14 Gm. in 49 da s. Nephritis th serious reaction most to be feared. Acetarsone has been super seded by safe d more effect ve agents.

See Da kison nd Birt (CanadMAJ 34 33, 1936) acetarsone as improvement over previous medicines Cole (J 108 824, 1937) toxic and curativ doses too close together; Robinson and Robinson (AmJSyph 23 168, 1939) unsaf ; Nyhus (be J 144 1637 1950) as good as ny tisyphilitic drug.

In older children from 6 to 8 years of age are found osteitis periostitis, interstitial keratitis, and involvement of the central nervous system. Peni cillin is highly effective for the cure of specific inflammation (Yampolsky and Heyman J 132 368 1946) but interstitial keratitis remains a problem despite the antibiotic Around puberty interstitial keratitis eighth nerve deafness and involvement of the central nervous system are the serious haz ards. Any of these requires the care of an expert.

INTERSTITIAL KERATITIS.—The routine use of a cycloplegic fever therapy and full doses of chemotherapy are of great value (Klauder and Vandoren

AOphth 26 408 1941) In 42% of their 532 cases the eyes were involved either simultaneously or within one month of each other The second eye in 79% was involved by the tenth year The final visual acuity of both eyes was good in 64% of the patients treated continuously as compared to 47% of patients treated intermittently or irregularly Arsphenamine treatment supplemented with fever therapy either malarial or artificial successfully prevented relapse in all but 1 of 55 patients so treated by Klauder and Vandoren. Penicillin in a dose of 50 000 units each 4 hours failed to prevent involvement of the second eye in approximately half of 72 cases even when fever was used in adjunct (Klauder AmJSyph 31 575 1947) The addition of penicillin did not improve the results of adequate treatment entailing 20 doses of arsenical and 8 to 10 bouts of fever Fever therapy by means of typhoid antigen and concomitant penicillin comprised good treatment in the opinion of Forsyth (SouthMJ 41 1015 1948) but proved to be not highly satisfactory in terms of clinical results wrote London and Noojin (AmJSyph 32 483, 1948) who expressed the wish that better treatment were known. Their wish was not long delayed in fulfillment





Fig 479 —A girl blind eye congenital syphilis (Cole J 109 580 1937)
Fig 480 —Mutilation produced by prenatal syphilis (Dr H N Cole)

In estigating the effects of ACTH and cortisone on variou inflammator d eases of the ey Steffensen t al (AmJOphth 33 1033, 1950) observed that a patient with i ter st tial k atitis after rece ving these medicines parent rally contin ed to improve whe cortisone wa used locall whil other patient treated only topicall with cortisone did w ll Woods (AmJOphth 33 1325 1950) reported marv lous results confirmed soon b man others, in luding H rne (BMJ 1 1289 1951) Simpson et al (J\DI 32 116, 1951) Crane and McPherson (AmJSyph 35 525 1951) and Madd n and Danto (ADS 64 437 1951)

Cortisone acetate suspension, diluted 1-4 with saline making 6 mg /cc, may be dropped into the eyes approximately hourly while the patient is awake Improvement is dramatic visible within 24 hours, practically complete subjectively within 96 hours. Cases treated before corneal vascularization heal completely and recurrent attacks are as responsive as primary ones. The effects are especially good in early cases (Woods AmJSyph 35 517 1951)

Thyroid in conjunction with cortisone and fever therapy appeared to be beneficial in some cases of Klauder and Meyer (ArchOphth 51 435, 1954) who found the BMR regularly to be low and who insisted on the necessity for treating the patient early in the inflammatory stage of his disease

Fever therapy was asserted as being of some benefit by Okala (AmJSyph 37 549, 1953) but penicillin is not, and the benefit of cortison and ACTH are only transient

be felt. Their influence on inflammatory or allergic reactions diminishes vascular congestion, retards early fibrosi inhibits phagocytosis and reduces the formation of new blood vessels, but does not affect the underlying disease pointed out Ashworth (BritJVD 29: 3 1933) A hworth reported remarkable relief of photophobia red eye and distress with cortisone therapy in 28 cases, and believed that, if the drug is used early the disease may be halted before corneal vascularization takes place If its use is begun after vascularization has started, more time i required to bring the case under control. Concurrent heavy dosage with penicillin wa recommended, and tentative withdrawal of cortisone were depended on to 1 termine the time when its use could be discontinued. Corneal grafting he stated, might be considered afte activity of the disease had been in abeyance for years.

EIGHTH NERVE DAMAGE is extremely resistant to therapy It represents a form of parenchymatous neurosyphilis and requires appropriate adequate antisyphilitic treatment

THE SPINAL FLUID must be examined early and, if this shows evidence of involvement of the central nervous system suitable modification and intensification of treatment must be devised.

Juvenile neurosyphilis is estimated and attacked as adult neurosyphilis is, the spinal fluid findings being significant criteria of activity of the disease Penicillin and fever therapy are effective in the meningovascular varieties, but juvenile paresis and tabes dorsalis have a poor prognosis (Menninger Juvenile Paresis, Williams and Wilkins, 1936 Dennie AAAS publ. #6 p. 111 1938 Nielsen et al ADS 46 688 1942)

PENICILLIN THERAPY.—See Platou et al (J 127 582, 1945) Rose et al. (JPediat 29 667 1946) 36 cases, no death from syphilis, Neilson et l (ADS 53 625, 1946) 30 cases, 1 death Heyman and T mpolsky (AmJDisChild 71 605, 1946) 22 cases, 3 deaths, 2 relapses Olansky and Beck (AmJSyph 31; 61, 1947) penicill lone compared with penicillin, arsenical and bismuth, Platou and Kometani (Pediat 1 608, 1948) penicillin results, especially in juvenile neurosyphilis; Barker (JPediat 32 616, 1948) Rose et al. (AmJDisChild 77 729 1949) 55 cases, 7 deaths.

DERMATOSES DUE TO FUNGI

DERMATOMYCOSES

The Mycoses are the diseases caused by fungi. While bacteria the Schizomycetes, are botanically members of the fungi diseases caused by them are considered in the preceding chapter. Bacteria seem to be almost wholly unrelated to other groups of fungi although some of the higher forms are suggestive of Myxophyceae which have lost their chlorophyll.

Schizomycetes are typically unicellular plants the cells are usually small and relatively primitive in organization. Higher fungi form a large heterogeneous group of plants including all those lacking chlorophyll. In most of them the vegetative body is surrounded by cell walls and usually appears as septate filament called hyphae. The vegetative hyphae are collectively known as mycelium. Hyphae grow by the sprouting of small protuberances, which enlarge round off and are cut off from the mother cells by septums. Daughter cells or sprout cells, are known as blastospores. Among the yeasts this is the only type of vegetative body. When growth conditions are unfavorable resting cells are formed, called chlamydospores. When circumstances become favorable the chlamydospores develop normal vegetative mycelium. Hyphae generally are intertwined in silky masses which generally are capable of absorbing food at any point. Various specialized structures develop from them. Most fungi, at certain ages and under favorable conditions of nutrition develop reproductive structures on the mycelium. These are usually spores. Spores are cells or groups of cells characteristically formed and able to grow independently into new individuals. In many fungi there is a sexual function involving the two processes fertilization, comprising the fusion of two nuclei, and miosis, in which there is a return to the single chromosome number. Some fungi live without such reconstruction of their nuclei and propagate themselves by imperfect stages only. Such fungi with incomplete or with incompletely known life cycles have been called *Hyphomycetes* or *Fungi imperfecti* (Dodge C. W. Medical Mycology Mosby 1935). Fungus dermatoses are due to fungi imperfecti. The ability to thrive on keratin distinguishes the few pathogens from the many nonpathogens in general (Gregory: BiolRev 10 303, 1003)

Botanical Classification of Fungi.—Fungi are divided into five orders characterized by the form of their vegetative body or thallus, and by their mode of reproduction, according to Brumpt (Précis de Parasitologie ed 6 Masson et Cie 1949)

- Myxomycetales—thallus without membrane protoplasm amoeboid, reproduction with spores (the slime molds)
- Hyphomycetales—thallus with membrane (mycelium) generally septate nonsexual reproductive bodies conidia present or absent.
- Ascomycetales—mycelium septate reproductive bodies nonsexual *spore formation* in specialized asci ascospores.
- Basidiomycetales—features like those of Ascomycetales but spore formation on specialized organs supporting basidiospores.
- Phycomycetales—mycelium nonseptate reproduction both sexual and nonsexual.

Of interest in this chapter are members only of the Hyphomycetales, Ascomycetales and Phycomycetales.

Hyphomycetales are divided by Langeron (preferred by Brumpt) among:

(1) *Microsiphon types*, with extremely fine and continuous mycelium, including the genera Actinomyces Nocardia and Streptomyces.

(2) *Thallospore types* characterized by the formation of thallospores by constriction of the thallus without particular differentiation subdivided into (*a*) arthrospore genera, in which arthrospores are produced by *fragmentary* disarticulation from the vegetative filament (chlamydospores are a kind of arthrospore) including the genera Cladosporium, Geotrichum, Hormodendrum and Trichosporon (*b*) blastospore genera, in which round or oval globules bud either from the ends of filaments or from the globules themselves including the genera Candida, Geotrichoides Pityrosporum Torula and Torulopsis and (*c*) aleurospore genera in which the thallospores are aleuries forming like chlamydospores united intimately with the mycelium, including the genera Glenospora and (according to Langeron) the dermatophytes Trichophyton Microsporum, Epidermophyton and Achorion.

(3) *Conidiospore types* which form true conidia, subdivided into (a) sporotrichial genera, in which true conidia simple or septate are isolated and inserted directly upon the mycelial filaments, including the genera Rhi ocladium, Sporotrichum and Trichosporon, (b) sporophore genera, in which conidia are carried as ach or as leuries at the extremities of simple or composite filament named sporophores including the genera Alternaria Acremoniella, Acremonium Cephalosporium, Cladosporium, Hormodendrum and Trichosporon and (c) phialides genera, in which the sporophore entire if it i simple or with all it ramifications if it is composite i isolated from the sterile egetative mycelium by a basal partition including the genera Aspergillus Penicillium, Phialophora and Scopulariops s.

(4) *Genera f uncerta n syst matic position* Coccidioides Cryptococcus Histoplasma, Madurella and Malassezia.

ASCOMYCETALES contain highly differentiated fungi with septate mycelium. They produce asques (little sacs) and arious forms of conidia; their pleomorphi m is marked. The asques develop in the ends of certain filament spoken of a fertile and the cells of these differentiate into a number of spores ascospores, ranging from to 12 in number i various species. These ascospores are surrounded by an internal membrane and an external membrane which latter may present a germinative pore Fertile filament along with other filament form a pseudoparenchyma from which spring organs of fructification, or perithecia. The fruiting bodies of some organisms are well developed rounded and closed, as i Aspergillus. The ascomycetic parasites are classed l y Brumpt in the f llowing groups

(1) *Hemiascomycetes* lacking perithecium, the bare asques carried at the en ls of filament i cluding (a) th Endom cetales with well-developed mycelium and asq es disti ct from the filame ts exemplified by the genus Endomyces, and (b) the Saccharomycetales, with rudimentary mycelium and asques resembling other cells, xemplified by the genus Saccharomyces.

( ) *Plectomycetes*, with closed perithecium, including two orders (a) Gymnoascales, in which the perithecial envelope is formed with loose filaments, among which Brumpt places the dermatophyte genera Achorion Ctenomyces Epidermophyton, Microsporum and Trichophyton, admitting them to be aberrant never having been observed to produce asques o ascospores (Langeron put these in the order Hyphomycetales), a d (b) Plectascales, in which the perithecial envelope is compact inclosing the closed perithecium and containing asques not disposed in parallel series, exemplified by the family Aspergillacea, with it genera correctly named Eurotium (Aspergillus) Diplostephanus (Sterigmatocystis) Carpenteles (Penicillium) Microascus (Scopulariopsis) and Allescheria (Scedosporium)

(3) *Pyrenomycet s* characterized by a stroma presenting bottle-shaped perithecia and asques enmeshed in the false parenchyma forming a hymenium at the base of the perithecia exemplified by the genus Piedraia.

PHYCOMYCETALES are characterized by their white o pigmented thallus which present transverse divisions only at the point of formation of reproduct ve organs. Reproduction may be sexual or asexual. When asexual, conidia are formed, are motile and are called zoospores, which are borne in a zoosperangium. When sexual, th equal male a d female elements unite by isogamy t form one zygospore or two unequal sexual elements unite by heterogamy to form one oospore. In the family Chytridiaceae of the suborder of Oomycetes, the mycelium is rudimentary or absent, and the genera include Coccidioides Paracoccidioides and Rhinosporidium.

History of Knowledge of Fungus Diseases.—Hooke i 1677 m de a lens which enabled h m to see filaments of the fungus productive of yellow spot disease in the damask rose Malpighi knew of plants which grow on the plants. In 1720 Michel wrote about many fungi and described Aspergillus. Linnaeus (1752) collected all the facts then known and named many species. The first importa t human pathogen to be seen was observed by Langenbeck (1839) that of thrush, d in the same year Schönlein found that of favus. Charles Robin in 1843 named Langenbeck s organism *Old um albicans*. Lebert named Schönlein's fungus *Oidi m schoenlei* and Remak hanged this to *Achorion*. In 1844 Gruby found fungi f ringw rm and differe tiated the large spore type from the small spore (See Edit. JTropMed 37 377 1934.)

GENERAL REFERENCES.—Castellani and Chalmers (Manual of Tropical Medicine, New York, Wood, ed. 3, 1920). Greenwood and Swartz (ADS 16 494, 1927), review and bibliography; Jacobson (Fungus Diseases, Thomas, 1932), Shaw (JLClM 20 113, 1934; 21; 242, 1935) abridged key t species of pathogenic fungi Dodge (Medical Mycology Mosby 1935), Swartz (KEngJM 215 332, 1936) history classification, clinical spects of fungus infections; Emmons (BotanRev 6 474, 1940), bibliography Langeron (Précis de Mycologie, Masson, 1945), Skinner et al. (Henrici Molds, Yeasts and Actinomycetes, Wiley & Sons, 1947); Lewis and Hopper (Introduction t Medical Mycology, Year Book Publishers, ed 3, 1948) Swartz (Elements of Medical Mycology Grune and Stratton, 1949), Brumpt (Précis de Parasitologie, Masson, ed. 6, 1949) Sutton and Sutton (The Mycoses, Tice Practice of Medicine 4 111, 1952, Prior Co., Hagerstown, Md.) Moss nd McQuown (Atlas of Medical Mycol gy Williams and Wilkins, 1953) Lacaz (Manual de Micologia Medica, São Paulo, 1953) Conant et al (Manual of Clinical Mycology ed. 2, 1954, Saunders) Simons (Medical Mycology Elsevie Amsterdam, 1954) Langeron (Mycologie générale, ed. 2 by Vanbreuseghem, Masson, 1954) Moss et al. (AD 71 248, 1955) fine illustrations of lassification, diagnosis, mycologic technics and features of fungus infections

Cultivation of Fungi and Ecology of the Diseases They Cause.—Fungi appeared to have been demonstrated by direct examination in over 500 cases of tinea reported on by Lewis et al. (SouthMJ 39 246 1946) yet cultures yielded negative results in some 33% of these The fungi that were grown were *Trichophyton mentagrophytes* in 37% *Trichophyton purpureum* in 26%

and *Epidermophyton inguinale* in 4%. To increase the likelihood of obtaining positive cultures and of obtaining at least some of them free of contaminants, Curry (BJD 61 54, 1949) made multiple miniature cultures using droplets of inoculum on one Petri dish in many small areas. The value of hanging-drop

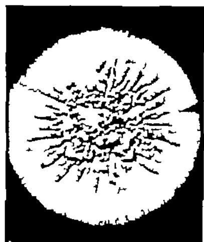
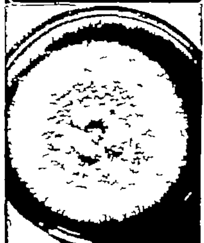
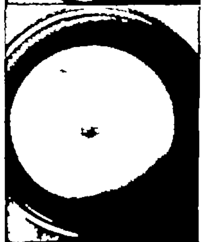



Fig. 583.—*E floccosum* (gul ale)

Fig. 586.—M ad mal.






Figs. 581 and 582.—*T mentagrophytes (gypseum)* smooth nd gran l

Fig. 585.—*T purpureum.*

Fig. 584.—M ca is (? sectors)

Figs. 581-586.—Giant colonies of common pathogenic fungi. (Drs. George M. Lewis and M ry Hopper.)

cultures has been attested by Blumenthal and Snow (J 107 1367 1936) and by Zimerinov and Rafalovich (ADS 61 94 1950) who obtained speedy out growth with mycologically diagnosticable features and described the features of the common pathogens.

Sabouraud's dextrose agar was amended by the addition of penicillin streptomycin and actidione by Georg (ADS 67 3.. 1953) who found these inhibitors of bacterial and saprophytic activity useful in obtaining fungus cultures from heavily contaminated material Success in isolating several pathogens from used shoes and from a shower stall was obtained by using a similar selective isolation medium reported Ajello and Getz (JID 22 17 1954)

The results of inoculations of human pathogens into animals were studied by DeLamater and Benham (JID 1 451 469 1938) Moore (Sci 89 514 1939) induced pathologic lesions of the chick chorioallantois, which provides a satisfactory culture medium for interesting investigations. *Trichophyton mentagrophytes* cultivated in increasing concentrations of pelargonic acid developed a tolerance of 6 times its original tolerance Murphy and Rothman (JID 12 5 1949) discovered. Solutions of the radioactive isotopes P^{32} and I^{131} are not self-sterilizing, for fungi lived in them unaltered as to cultural characters and pathogenicity reported Pearson et al. (JBact 56: 397 1948)

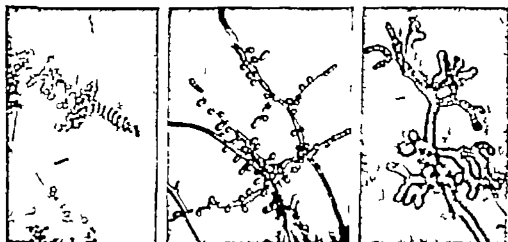


Fig. 557—*Trichophyton mentagrophytes (gypseum)* spirals are characteristic.

Fig. 558—*Trichophyton tonsurans* microconidia may be attached or unattached, singly or in clusters, and are seen in many species of fungi

Fig. 559—*Achorion schoenleini* favic chandeliers are characteristic.

Figs. 557-559 Courtesy of Drs. George M. Lewis and Mary Hopper

Species of *Trichophyton gypseum* were found on farmyard dung as a natural habitat on a farm where the calves had ringworm (Muende and Webb ADS 36 987 1937) while positive cultures were obtained from shoes, which apparently served to reinfect the wearers, by Jamieson and McCrea (ADS 44 837 1941) *Microsporum gypseum* infections (q v) and histoplasmosis (q v) may come from the soil.

In searching soil samples for *H capsulatum* with the membrane filter technic, *M gypseum* was obtained from the earth near a farmhouse in Tennessee by Gordon (JID 20 201 1953)

The incidence of varieties of fungus infections as related to geographic location was considered in a review of many cases occurring in St. Louis, Springfield, Mo., and Oklahoma City by Sisk et al (ADS 68 681 1953)

A study of British Army subjects indicated that when tinea of the body and the feet coexisted in a patient, they were usually due to the same organism the corporeal infection evidently being acquired from the patient's feet (Sanderson and Sloper BJD 65 362, 1953)

Methods of Cultivating Fungi and details of their botanical features are to be found in the treatises listed under general references notably those of Brumpt Conant et al Dodge Jacobson Langeron, Lewis and Hopper Moore et al., and Swartz.

See Weidman (J 60 499, 1928) 15 varieties of dermatophytes found in American cases, 50% of which were due to *T interdigitale*; Emmons (ADS 30 337, 1934) culture cell, bovine horn medium, formation of conidia, Davidson and Gregory (CanadJRes 10 373, 1934) organisms while normally parasitizing host produce hyphae and thallospores, while on detached tissues in vitro produce *highly differentiated spore forms*, a saprophytic phase of possible epidemiologic significance; Conant (ADS 33 665, 1936; 36 781, 1937) cultural studies of genus *Microsporum*; Shaw (JLCM 20 113, 1934; 21 244, 1935), classification and cultural characters, Williams (ADS 36 581, 1937) subsurface growth features of dermatophytes, Peck and Rosenfeld (JID 1 237 1938), pH of cultures and influence on growth, valeric acid inhibition not due to pH Williams (ADS 38 236, 1938), incorporation of dyes in medium to improve culture results; Epstein (JID 1 141, 1938), identity and range of variations of *T interdigitale* and *T gypseum*; Downing et al (NEngJM 222 363, 1940) demonstrable incidence of dermatophytes in suspected dermatoses, direct and cultural methods both necessary, Cornbleet and Meyer (NEngJM 230 604 1944) growth of fungi in sweat, Emmons and Hollander (ADS 52, 257 1945) speciation and mutation Duncan (BMJ 2 715, 1945) incidence of all types of *fungus disease in Great Britain*; *Lewis and James* (ADS 53 481, 1946) at pH 10.6 saprophytes are mainly inhibited but dermatophytes are not; Weidman and Glass (ADS 57 300, 1948) technic of demonstration by scrapings, Kimerinov and Rafalovich (BJD 60 238 1948) hanging-drop culture technic and features of common fungi so grown Nomenclature of Fungi Pathogenic to Man and Animals (Med. Res. Council Memo. 23, London, H.M.S.O., 1949) Wilson and Plunkett (Pract 163 323, 1949) simplified practical laboratory methods Curry (BJD 61 54, 1949) droplet culture method of isolation; Walker (JID 62 239, 1950) epidemiology of dermatophytoses in Great Britain Lowenthal (ADS 63 761, 1951), effect of ionizing radiation on *M canis* little change resulting from 600 r Lewis et al (ADS 63 622, 1951), simple guide for laboratory methods of mycologic study; Brueck and Buddingh (PSExpB 76 258, 1951) yolk sac propagation of pathogenic fungi.

Mycotic Diseases are by no means limited to the skin but their conspicuous manifestations are often cutaneous. See Lewis and Hopper (Introduction to Medical Mycology ed 3 1948)

Dermatomycosis includes all cutaneous infections due to fungi.
Dermatophytosis is applicable to superficial infections.
Epidermophytosis implies infection with an *Epidermophyton*.
***Trichophytosis** is similarly limited to parasitism with a Trichophyton.*

Bilateral, superficial, circumscribed, erythematous and scaly eruptions of the upper parts of the inner aspects of the thigh are commonly caused by *Epidermophyton cruris*. One may often correctly suspect that an infection of the scalp is caused by *Microsporum canis* from the history of contact with an infected animal, the short duration, the tendency to heal spontaneously and the inflammatory character of the lesion. Infection of the skin due to *Candida albicans* and the lesions of blastomycosis, actinomycosis and sporotrichosis are usually expressed clinically in fairly characteristic ways. One may often recognize a *Trichophyton purpureum* infection from clinical inspection alone (Lewis and Hopper ADS 35: 461 1937) However the diseases produced by closely related organisms may not be distinguishable clinically It is practical to discuss dermatomycoses according to their sites.

Human Pathogens, with their identifying features (Lewis and Hopper)

Direct examination in these descriptions, usually refers to the microscopic appearance of the organisms in a specimen mounted in 10% aqueous solution of potassium hydroxide.

Cultural characteristics are as seen after isolation on a solid medium containing 4% crude American dextrose 1% Fairchild's peptone and 1.8% agar

Culture mount refers to the microscopic appearance of a cultural growth as seen in a hanging-drop preparation, in a Henrici slide culture, or in a direct mount from a culture of material in 10% potassium hydroxide solution The last type of mount is not advisable for routine use because so prepared, the arrangement of fungus elements cannot be studied satisfactorily

Microsporum audouini (commonly causative of tinea capitis in children)

Direct Examination.—Short, broken-off hairs are extracted for examination. The spores are round, small, and grouped to form a mosaic sheath around the infected hairs There is usually no tendency to the formation of chains.

Cultural Characteristics—The colony is slow-growing, consisting of close-matted, velvety aerial mycelium, light gray to brown in the center with radiating furrows. The reverse of the colony is reddish brown to orange in color

Culture Mount—Fuseaux and microconidia are occasionally seen Chlamydospores and pectinate bodies are frequent

Microsporum canis (M lanosum) (commonly causative of tinea capitis in children)

Direct Examination—Hair infected with *M canis* cannot be distinguished from hair infected with *M audouini* In scrapings from lesion of tinea circinata, segmented mycelium may be noted

Cultural Characteristics—The growth appears first as a downy fluff, and it develops fairly rapidly After 1 week the colony is woolly and the aerial material is abundant The color is buff tan This development of yellow pigment on the undersurface of the colony is characteristic Grooves may be radial or concentric Pleomorphism begins after 4 or 5 weeks. The appearance under the filtered ultraviolet rays (Wood light) is distinctly lavender blue or shell pink toward the center of the colony the colors being bright and clear

Culture Mount—The feature of this fungus is the presence of large numbers of fuseaux of the tapering sort. Microconidia and some other forms may also be noted.

Microsporum gypseum (M fulvum) (Tinea corporis and capitis, often kerion)

Direct Examination—A hair infected with *M fulvum* may resemble in appearance hair infected with any other *Microsporum* Sometimes spores in linear arrangement may be observed

Cultural Characteristics.—The growth is flat, floury and cinnamon brown. A central umbo may be present Concentric furrows sometimes appear Pleomorphism is usually manifest after several weeks The reverse of the colony is reddish-brown to orange in color

Culture Mount.—Numerous fuseaux are present. Racquet mycelium, nodular organs, and small round spores may also be seen.

Trichophyton sulfureum (tees rans) (nonfluorescent tinea capitis in adults)

Cultural Characteristics.—At first, the colony is velvety with a central red nodule the rest of the culture showing a delicate primrose color. Later it becomes powdery, folded with a small central crater and becomes sulfur yellow in color.

Trichophyton (Achorion) schoenleini (Favus)

Direct Examination.—Large spores in chains are noted in the substance of the hair. The presence of air bubbles is almost of diagnostic significance. Sporulated mycelium will be found in large amounts in scutula but such mycelia are few in number in infected nails or in superficial lesions of the smooth skin.

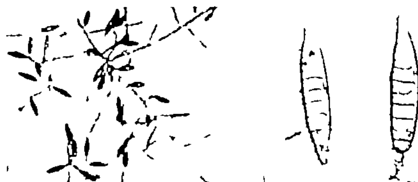
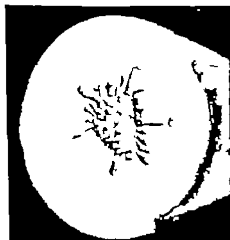


Fig. 590.—*M. gypseum* macroconidia, or fuseaux, attached to the hyphae indicate either *M. gypseum* or *M. canis.*

Fig. 591.—*M. canis*: detached macroconidia, showing septations. (Drs. George M. Lewis and Mary Hopper.)





Figs. 592 and 593.—*Microsporum gypseum* giant colony and culture mount stained with lactophenol-cotton blue. (Dr. Emanuel Muskatblit.)

Cultural Characteristics.—After 3 or 4 weeks the growth is smooth, compact and waxy. The surface shows numerous folds. Pleomorphism is rare. The submergence of the colony usually results in cracking of the agar.

Culture Mount.—Favic chandeliers may be noted. Chlamydospores in large numbers may also be observed.

Trichophyton mentagrophytes (gypseum) (Tinea especially of feet and nails)

Direct Examination.—In follicular infection, small, round spores in chains may be found external to the hair. In scales, macerated tissue, or in nail scrapings, chains of spores or segmented mycelium with little branching will be noted.

Cultural Characteristics.—There are 4 types of growth which Lewis and Hopper believe are closely related genetically.

1. The usual type. This begins as a white, fluffy growth. After about 2 weeks, the surface becomes velvety and buff-colored. There is usually a boss at the center and a few irregular folds.

2. *The granular variety.* The surface is powdery and is light buff or maize yellow in color. Fluffy changes develop with age.

3. *The T. interdigitale type.* This begins as a downy projection, developing into a white, fluffy, diffuse growth covering an agar slant within 2 weeks.

4. *The T. ... type.* This is white and fluffy at first, later becoming compact. Surface irregularities are present.





Fig. 594.—*T. schoenlei*, giant colony. (Dr. D. Muskatblit.)
Fig. 595.—*T. concentricum*, colony in test tube. (Dr. E. Muskatblit.)





Fig. 596.—*T. mentagrophytes*, slide culture, showing microconidia and fuseaux. (Dr. D. Muskatblit.)

Fig. 597.—*T. mentagrophytes*, slide culture, showing microconidia and spirals. (Dr. D. Muskatblit.)

Culture Mount.—

1. The usual type. Spirals may be seen. Small numbers of fuseaux and nodular organs, pectinate bodies, racquet mycelium, and chlamydospores may be noted. Microconidia are present.

2. The granular type. Numerous fuseaux are present and dense masses of microconidia are to be seen. Few spirals will be seen. Chlamydospores and racquet mycelium may be found in the subsurface growth.

3. The T. interdigitale and T. ... types. A large number of filaments and a few clusters of microconidia are observed. Nodular organs and racquet mycelium may be found. Spirals and fuseaux are usually absent.

Trichophyton rubrum (purpureum) (Tinea)

Direct Examination.—There is nothing characteristic in the microscopic appearance of the fungus in scrapings. While the amount of fungus material may be sparse, large numbers of organisms have been noted in an occasional specimen. The mycelium is about the same size as that of *T. gypseum* being 3 or 4 microns in diameter.

Cultures.—On dextrose agar primary growth at first is fluffy, pure white and hemispherical. The edge of the colony becomes less fluffy and at times is granular. The under surface of the colony shows the typical rose-purple color which gradually spreads to the edge of the colony and may be noted in varying degrees throughout the colony. Pleomorphism occurs eventually. Under filtered ultra violet rays (Wood light) the cultures show colors which are bright but hazy. The central half of the colony is mauve, the remainder is a light, soft blue-violet. There are many sterile (septate) hyphae and many microconidia in thyrses and in grapelike clusters in culture mount. Fuseaux are few. Chlamydospores develop in older growths. Inoculation of animals is occasionally successful. The index of sensitization is low.

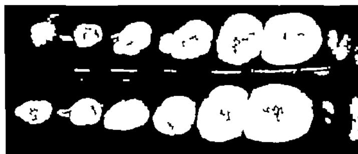


Fig 398.—*Candida albicans* cultures. (Dr. L. Moskatblit.)





Fig 399.—*C. albicans* culture mount, lactophenol-cotton blue stain, showing hyphae and blastospores. (Dr. L. Moskatblit.)

Fig 400.—*C. albicans* culture mount, showing hyphae, blastospores and chlamydospores. (Dr. L. Moskatblit.)

Trichophyton violaceum (Tinea)

Direct Examination.—Large spores in linear arrangement may be seen invading the shaft of an infected hair or in scales or nail tissue.

Cultural Characteristics.—The colony is compact, smooth, and shiny, and it has a typical deep violet color. The surface shows convolutions. Pleomorphism is rare.

Culture Mount.—The mycelium shows irregular and oddly shaped branches. No free or attached spores are developed. Chlamydospores are seen in older colonies.

Trichophyton tonsurans (crateriforme) (Tinea)

Direct Examination.—Large spores in chains are seen in the shaft of the infected hair usually in large numbers.

Cultural Characteristics.—The growth is compact, creamy white, and velvety. The central portion is broken and depressed, being yellow. Pleomorphism is rare.

Culture Mount.—Conidia in clusters (grapes) or on stalks (thyrses) are to be noted. Chlamydospores are common.

Candida (Monilia) albicans (Moniliasis)

Colonies originate by bipolar sprouting of blastospores and the pseudomycelium is composed of ellipsoidal cells. The colonies are creamy, thick and convex. *Candida albicans* is a "yeastlike" fungus, *differing from a true yeast in that a pseudomycelium is formed, whereas* true yeasts reproduce by budding, and the daughter cells do not adhere to the mother cell.

Cultures.—The growth is smooth, pasty and cream-colored, and it grows rapidly on dextrose medium. The central portion later appears honeycombed. On corn-meal agar mycelium, characteristic spore clusters, and chlamydospores develop. *Ascospores are not formed.*

Agglutination Reaction.—The organism agglutinates in a serum prepared against *Candida albicans* (Benham, J.Infect.D. 49: 183, 1931).

Animal Inoculation.—Benham (1931) found that the intravenous injection of 1 cc. of a 1:1000 suspension of a live culture killed a rabbit in 4 or 5 days. Abscesses in which *Candida albicans* may be recovered develop in the kidneys and other organs.

Differential Diagnosis.—Cryptococci do not develop mycelium, and other species of *Candida* may be distinguished from *Candida albicans* by the absence of chlamydospores when grown on corn-meal agar. *Mycoderma* may usually be recognized by its growth appearance in culture; a culture mount reveals arthrospores. *Endomyces* and *Saccharomyces* form ascospores; the former also develops mycelium.

Epidermophyton floccosum (Inguinale)

Direct Examination.—The scales contain chains of spores in which the elements tend to be flattened. The amount of fungus material is often plentiful.

Cultural Characteristics.—After 2 to 3 weeks the growth is apparent. It develops a velvety surface with irregular folds and is characteristically grayish olive drab or greenish drab in color. Pleomorphism develops early.

Culture Mount.—Fuseaux of the blunt-end variety are to be seen in groups. Chlamydospores and racquet mycelium may also be observed.



Fig. 401.—*C. albicans* in KOH preparation of a scale, ×770. (Dr. F. Muskatblit.)

Malassezia furfur (Microsporum furfur) (Tinea versicolor)

Direct Examination.—Fungus elements are usually present in profusion, and the picture is characteristic. They consist of round or ovoid, refractile spores in clusters. Mycelia, fairly long but fragile, occur in considerable numbers.

Culture.—Doubtfully successful. See Tinea versicolor.

Nocardia minutissima (Actinomyces minutissimus) (Erythrasma)

Direct Examination.—On examination with the high power of the microscope fine threads may be noted. If the oil immersion lens is used, the threads are visible, being *long*, tortuous, and interlacing. A few spores may be seen.

Cultural Characteristics.—There is not general agreement that this microorganism has been cultured.

Trichophyton concentricum (Endodermophyton tropicale) (Tinea imbricata)

Direct Examination.—Numerous segmented hyphae are noted.

Cultural Characteristic.—The growth is compact and gray to brown in color, and it shows an uneven surface. Superficial resemblance to *A. kerion schoenleini*.

Culture Mount.—Vegetative forms may be noted. Microconidia are not present.

Actinomyces bovis (Actinomycosis)

Direct Examination.—This is the most important laboratory investigation of a patient *suspected of infection with this microorganism.* The granules are seen to consist of one or more colonies in which in the mid-zone there is a mass of twisted mycelium, and at the periphery a palisaded arrangement of hyphae forming a fringe. These latter organs are enlarged at one end and are striated. The ray fungus is gram-positive. The central mycelium takes the basic dye and the periphery alone takes the acidic dye.

Cultural Characteristics.—There is considerable difficulty in obtaining a cultural growth, and it usually dies quickly. The colonies are pasty but of variable consistency and configuration.

Culture Mount.—Sterile mycelium without characteristic spore forms.

Monosporium apiospermum (Maduromycosis)

Cultural Characteristics.—Rapidly growing colony produces a white, cottony aerial mycelium which later turns gray or becomes buff to brown in color

Cultural Mount.—Ovoid and pyriform conidia, 3 to 10 microns long by 5 t 7 microns wide re produced singly t the ends of long conidiophores or from the ides of the mycelium on short conidiophores.



Figs. 402 and 403.—*F. floccosum* culture mount, lactophenol-cotton blue stain. Fig. 402 shows fuseaux. Fig. 403 shows chlamydospores. (Dr E. Muskatblit.)

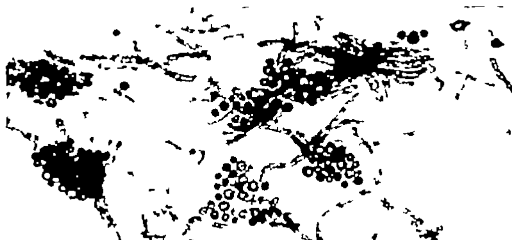


Fig. 404.—*M l vesse furfur* from tinea ersicolor polychrome methylene blue stain. ×770 (Dr E. Muskatblit.)

Rhinocladium (porotrich m) schenckii (Sporotrichosis)

Direct Examination.—Cigar-shaped cells may be noted, but fu gus material is usually absent.

Cultural Characteristics.—After 2 weeks, a moist growth is noted which is light brown in color but with age it becomes dark brown. The central portion shows irregula foldings. White excrescences form on the surface

Culture Mount.—Pea-shaped conidia re situated irregularly along the mycelium and rranged also as terminal triads and tetrads

Blastomyces dermatitidis (North American Blastomycosis of Gilchrist).

Direct examination.—Singly budding, thick w lled, round or oval, granula cells, 8 to 20 *microns in diameter* to be found.

Cultural Characteristics.—The central portion of the colony is gray and smooth becoming white and filamentous. A peripheral moist zone is usually present. Yeastlike growths are obtained on blood agar.

Culture Mount.—Microconidia, chlamydospores, and racquet mycelium may be noted. Budding cells may be obtained from the yeastlike growth.

Coccidioides immitis (Blastomycosis of Rixford and Gilchrist)

Direct Examination.—The microorganism is a sphere with a doubly contoured capsule from 5 to 60 microns in diameter and it contains 4 t 20 endospores.

Cultural Characteristics.—The growth is white and filamentous a brownish shade develops with age.

Culture Mounts.—Septate mycelium is profuse. Arthrospores and chlamydospores may be distinguished.

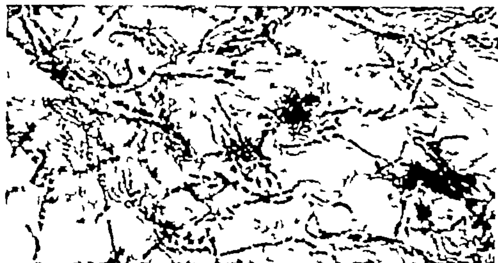


Fig. 605.—*Nocardia minutissima* from erythrasma, polychrome methylene blue stain, ×770. (Dr. L. Muskatblit.)

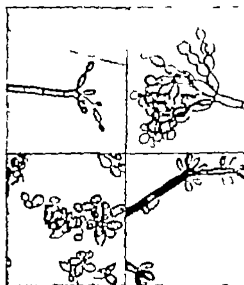


Fig. 606.—*Hormodendrum pedrosoi.* Above, Dendroid spore heads from corn-meal agar slide culture. *Lower left,* spores dissociated from conidiophore. *Lower right,* acrotheca type of sporulation. (Emmons, Hailey and Hailey J 116 25, 1941.)

Cryptococcus neoformans (Torula histolytica) (Torulosis)

Direct Examination.—Various-sized budding cells will be seen. A wet India-ink preparation reveals wide capsul

Cultural Characteristics.—The colony is moist and cream-colored, later changing to yellow and then to brown.

Culture Mount.—Round or ov l various-sized budding cells (India ink technic); no mycelium or ascospores.

Paracoccidioides brasiliensis (South American Blastomycosis)

Direct Examination.—Single and multiple budding, thick-walled yeastlike cells, 10 to 60 micron in diameter re found.

Cultural Characteristics.—Slow-growing, heaped, membranous or wrinkled colony with a short nap of white aerial mycelium which tends to become brown with age.

Culture Mount.—A few sessile oval to round conidia may be seen in culture at room temperature. Single and multiple budding, yeastlike cells may be seen in culture at 37° C.

Hormodendron pedrosoi (Chromomycosis)

Direct Examination.—So-called sclerotic cells of Medlar are present. These may be septate and are usually in groups. Small septate filaments may also be noted.

Cultural Characteristics.—The growth is compact, limited, and felty. Concentric zones may be colored brownish olive, olive black, olive gray and gray.

Culture Mount.—Olive brown spores are borne on conidiophores. Disjunctors are also usually present.

Phialophora verrucosa (Chromomycosis)

Direct Examination.—Single or clustered, round, thick walled, dark brown bodies which multiply by splitting, not by budding, not distinguishable from *Hormodendrum pedrosoi*.

Cultural Characteristics.—Slow growing colonies dark brown in color are found.

Cultural Mount.—Conidia arising from cups at the tip of flask-shaped conidiophores borne terminally or laterally singly or in groups, on the aerial mycelium.

Histoplasma capsulatum (Histoplasmosis)

Direct Examination.—The specimen, blood, urine, sputum or material aspirated from lymph node, marrow or spleen, should be mounted both unstained and stained by Giemsa method. The microorganisms, 2 to 4 μ in diameter are round, oval or yeastlike, usually budding, sometimes to be found in endothelial leukocytes.

Cultural Characteristics.—On dextrose agar incubated at room temperature, the colony is brown and glabrous, with an irregular surface, grows slowly and assumes a white cottony appearance with age, especially if the medium becomes dry.

Culture Mount.—Septate, branching hyphae with large, thick-walled chlamydospores showing tuberculate sculpturing of the outer wall, are found. These chlamydospores are best demonstrated in the mycelial cultures which develop on blood agar incubated in sealed tubes at 37° C. They best distinguish the organism from *B. dermatitidis*.

Rhinosporidium seeberi (Rhinosporidiosis)

Direct Examination.—Round to ovoid spores, 7 to 9 μ in diameter and spore-filled sporangia are found.

Pityrosporum ovale (? Seborrheic dermatitis, q. v.)

Direct Examination.—Flask-shaped cells of 2 to 10 μ, with or without budding, are seen.

Demonstration of Fungi.—One extracts a whitish hair stump or tears off the cap of a blister and immerses this in 10% aqueous potassium hydroxide. After maceration the bit is crushed under the cover slip and dim light is used in examination. Experience is necessary for distinguishing hyphae and spores from droplets of fat, epithelial cells, and detritus.

If 5% sodium lauryl sulfate is used as a clearing agent, instead of KOH, the material after direct examination may be used successfully for cultures (Mandel et al.: JID 18: 61, 1952).

Fungi may be stained in paraffin sections of tissues, fixed by any fixative, by means of the Hotchkiss-McManus periodic acid-Schiff staining technic. As performed at the University of Kansas Medical Center this involves the following steps.

(1) Deparaffinize to water. (2) Immerse in 0.5% freshly prepared periodic acid solution for 5 minutes. (3) Rinse with distilled water. (4) Immerse in Schiff's reagent (water-clear, not pink) for 15 minutes. (5) Rinse 3 times for 2 minutes each time in sulfurous acid. (6) Wash with running water for 3 to 5 minutes. (7) Counterstain lightly with alum hematoxylin for 20 to 30 seconds. (8) Rinse with tap water, dehydrate through 95% and absolute alcohol, clear in xylol, and mount.

Preparation of Schiff reagent. Weigh 1.0 Gm. basic fuchsin and 1.0 Gm. anhydrous sodium metabisulfite. Boil 200 cc. distilled water, add the fuchsin while stirring. Cool to 50° C., filter, then add 20 cc. 1N HCl. Cool to 25° C., then add the sodium metabisulfite. Ripen for 2 days in the dark at room temperature until straw color, filter through activated charcoal to remove color. Store in refrigerator.

Preparation of sulfurous acid. Measure 6.0 cc. of 10% aqueous solution of sodium metabisulfite, 5.0 cc. 1N HCl, and 100 cc. distilled water. Mix, stopper tightly, store in refrigerator. This is good for only 1 week.

Crystalline periodic acid may be obtained from G. F. Smith Chemical Co., Columbus, Ohio.

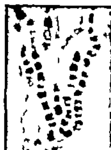
The Hotchkiss-McManus Schiff stain was modified for applicability to scales and hairs by Moskowitz et al. (ADS 67: 507, 1953) as follows: (1) dry the material in a film of albumen-glycerin mixture on a slide for a few hours at room temperature; (2) immerse in 95% alcohol for 2 minutes, followed by (3) 5% aqueous periodic acid for 7 minutes; (4) rinse in water 2 minutes; (5) stain in Schiff reagent 7 minutes; (6) rinse in tap water 2 minutes; (7) dehydrate through 95% alcohol, then absolute alcohol, then xylol, for 2 minutes each, and mount.

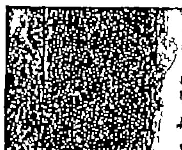
Periodic acid serves to transform the polysaccharides of the cell wall of the fungus into polyaldehydes. Where these aldehydes are present, there develops a deep, red color in the presence of leukofuchsin provided by the Schiff aldehyde reagent. Fungus elements so stained stand out sharply against a pale pink or colorless background.

Fungi may be stained with cotton blue dye by heating the scales on a slide in a drop of the following mixture (Swartz and Conant: ADS 33: 291, 1936): lactic acid, 1.0; phenol crystals, 1.0; glycerol, 2.0; cotton blue (C4B Poirrier), 0.5%; water, 1.0.

Kligman (ADS 63: 25, 1951) suggested the application of 10% potassium hydroxide to the skin before scraping, for then it becomes easy to demonstrate the organisms. Kligman et al. (J 146: 1563, 1951) described improved technic for diagnosing ringworm infections, using basic fuchsin rather than KOH.

Berberian (ADS 36: 1171, 1937) used this staining technic. Cover scales in small bits with 50% glacial acetic acid in water and dry in incubator causing adherence of scales to slide; defat by flooding with ether several times, with acetone several times, with alcohol in diminishing concentrations; stain in Martinotti's toluidine blue; wash in water; differentiate with 0.5% acetic acid; dehydrate in absolute acetone; pass through xylene; mount in Euparal or balsam.





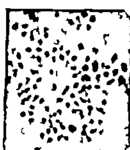


Fig. 607.—*Trich phyton* stained mycelium. (Dr B. B. Beeson.)
Fig. 608.—Tinea capitis, endothrix fungi in hair (Dr Stuart W y)
Fig 609.—*M* *and* ni, from tinea capitis. (Dr B. B Beeson.)





Figs 610 and 611.—Tine orga isms in KOH preparations of scales from dermatomycotic lesions. (Dr Emanuel Muskatblit)



Fig. 612.—*T rubrum* in scale from tinea cruris, stained with polychrome methylene blue ×850 (Dr E. Muskatblit)

An excellent method of staining fungi in scales or hairs is that of Muskatblit (ADS 59 1930 1949): Scales are broken into small fragment hairs are intact but separated from one another Raw egg white is applied to slide and the material transferred to the sticky surface while wet Dry in air or over a flame Defat and fix with Carnoy fluid (glacial acetic acid 10 parts, chloroform 30 and absolute alcohol 60) for five minutes; pour off fluid and dry Stain with polychrome methylene blue for 5 minutes, pour off and wash in water for 1 or minutes. Decolorize with 1% aqueous acetic acid for about 1 minute; this step is delicate and overexposure to acid will decolorize everything Wash with water minutes then absolute alcohol 5 minutes, and follow with xylol and balsam or Clarite

Hairs may be examined as follows The diseased stump is put on a slide, and washed with ether to defat It is then treated with aniline gentian violet solution for 5 minutes, blotted, treated with potassium iodide solution from 1 to 5 minutes, blotted, treated with aniline oil, then a mixture of equal parts of aniline oil and dilute hydrochloric acid to decolorize finally with aniline oil followed by xylol; then it is mounted in balsam.

See Keeteven (IJD 49: 500 1937) instead of KOH use 0.5% trinitrophenol in equal parts of phenol and oil of cloves; Bernhardt (ADS 48 532, 1943) permanent stained preparations, technic Wilson (ADS 52 207, 1945) permanent slides of cultures; Kligman and Mescon (JBact 60 415, 1950), modified Hotchkiss-McManus stain technic for tissues Hoffmann (DZtsch 76: 370 1936) staining of M. in tissue as Ajello (J 146 1581 1951), demonstration technics; Sharvill (BJD 64 329 1952) periodic acid Schiff stain Kligman et al. (AmJClinPath 21 89, 1951) Hotchkiss-McManus technic; Mescon et al. (Cancer 13 310, 1953) fungi in human neoplasms are saprophytes; Muskatblit et al (ADS 67 307 1953), Hotchkiss-McManus technic; Taschdjian and Muskatblit (ADS 68 570 1953) staining of KOH-cleared material; Lewis and Hopper (AD 7 302, 1936) histologic sections of colonies.

Mosaic Fungus, so called is perhaps not fungus at all, for it dissolves in ether absolute alcohol and phenol. It seems to be a degeneration product (Dowding and Orr ADS 33 865 1936) for mosaic material and *T gypseum* in transition forms appear in contiguity in mycotic scales. During healing of tinea, mosaic fungus increases and living fungus diminishes (Swartz and Conant ADS 33 291, 1936) The mosaic material after prolonged clearing in strong KOH appears to consist of notched crystals of cholesterol (Davidson and Gregory J 105 1262, 1935) It may appertain to imperfect keratinization (Cornbleet et al ADS 48 282, 1943) Finding it incapable of being cultivated and also soluble in various fat solvents Gotz (AfDuS 187 61 1948 188 104 1949) adjudged the mosaic substance to be a lipid present in various amounts normally in the palms and soles. Dowding (ADS 66: 470 1952) denied however that the mosaic substance is either cholesterol or something alive but thought it the product of the fungus, an extracellular deposit resulting from the dermatophyte It can be found on all normal feet sometimes on hands, and its presence is not necessarily secondary to the presence of mycotic infection stated Götz (ADS 70 119 1954)

Fluorescence in Demonstration of Fungous Infections.—Wood's light is ultraviolet light of wave lengths close to 3650 A.U which pass a Wood's filter made of glass containing nickel oxide. Exposed to this light in a darkroom the stumps of hairs infected with *M canis* and *M audouini* can quickly be differentiated by their bright, clear bluish-green fluorescence. Since these pathogens are the usual ones the test is practical (Lewis and Hopper ADS 34 681 1936) It affords an invaluable means for surveying numbers of children so as rapidly to identify the infected ones.

The fluorescent material in hairs infected by microspora can be extracted with hot water and is quenched by potassium iodide in 10% concentration, so that previous application of iodine may hide an infection without influencing the viability of the organisms (Fischer JID 13 139 1949) The fluorescent substance was extracted by boiling in water from which it dried as a white powder reported Robinson et al. (ADS 68: 129 311, 1953) The substance is destroyed by strong acids and bases. Its maximum fluorescence at pH 6.5 It is reversibly oxydizable. It shows a wide distinct band on spectrography maximum at 490° A.U It does not appear when fungi are grown on artificial media, even if various amino acids are added. Its presence is not proof that the fungus is viable for hairs long removed from the scalp and containing only nonviable fungi still manifest fluorescence.

TINEA

Symptoms.— Tinea (ringworm) is infection of the skin, hair or nails produced by various fungi Such infections are common and are at times serious. The ability of dermatophytes to grow on keratin forms the basis of their parasitic relationship with the human host. Sensitivity to dermato-

phytin in superficial mycotic infections, as well as in deep ones, is almost constantly present. There are analogies between the immunologic biology of dermatomycosis and of tuberculosis. Infectious diseases in general are characterized by the appearance of a primary lesion at the site of inoculation and



Fig 613.—Tinea corporis, due to *M can* the sort of "ringworm a hild is likely to contract from an infected pet

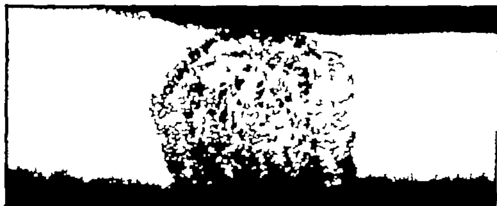


Fig. 614—Tinea of forearm. (Dr Robert N Andrad)

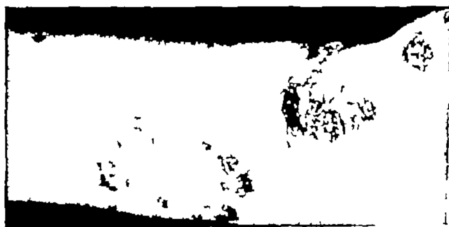


Fig. 615.—Tinea of forearm and wrist due t *T ment grophytes* (D J Lamb Calloway)

by the appearance of lesions of the skin under allergic conditions. Such latter dermatoses comprise the ids. Allergy is the sine qua non of their existence During the existence of a trichophytid the trichophytin reaction is positive

Environmental circumstances influence the equilibrium of the parasitic relationship so that the fungus may thrive or the tissues prevail. *Moisture*

warmth darkness and traumatic or chemical irritation favor the fungus. Ventilation coolness and dryness favor the tissues, as, of course do débride ment (washing) nonirritating antiparasitic chemicals and avoidance of in jury Clinical disease is often a composite representative of fungus infection and in addition secondary infection focal bacterial infection chemical damage from contactants, including medicinal substances, or the nutritional aberra tions which promote lichenification (p 870)

Clinical Classification.—In general clinical infections with fungi may be considered individually with clinical satisfaction without regard to systematic botany Pathogenic fungi causative of tinea damage only the skin even when they have been injected intravenously As a rule they damage the skin only superficially Nevertheless, their activity results in humoral alteration, and tinea, like many other dermatoses is by no means a purely cutaneous phenom enon.



Fig. 416.—Tinea corporis.



Fig. 417.—Tinea of axilla.

Clinical Forms.—One sees lesions of the following forms vesicular scaling macular macerated, fissured, papular callous, keratotic and lichenified (White ADS 15 387 1927) The nails are often infected and they may serve as a reservoir of reinfection difficult to eliminate.

Animal and Human Types of Tinea.—Fungi which are pathogenic principally to animals are likely to cause in animals lesions which are not very deep and inflammatory disease which is readily transmissible from animal t animal, lesions which contain numerous organisms easy to demonstrat lesions which are difficult to cure The same organisms in the human being may produce deeper and more inflammatory lesions, strong reactivity to trichophytin disease which is not readily transmissible, lesions in which organisms are few and demonstrable with difficulty and lesions which tend toward spontaneous cure or are comparatively easy to cure. Fungi which are pathogenic principally to human beings tend to cause chronic resistant, noninflammatory disease in human beings, and in animals to cause deeply inflammatory lesions. The distinction between animal and human infections is onl b rough analogy

Tinea Corporis.—Tinea of the glabrous skin usually begins with flattened, reddish papules. The lesions tend to spread peripherally and to heal in the center so that annular patches of dermatitis evolve In dermatophytosis, a state of resistance to inoculation with more of the same organism exists in the healed zone although areas outside the margins of these patches are vul nerable. The central portion is pinkish and has a superficially scaling surface. The margin is sharply defined, slightly elevated, actively inflamed, more or less scaly and often vesicular in places. The lesions gradually enlarge. Occasionally they coalesce, giving rise to arcuate figures. They may disappear spontaneously leaving no trace The tendency to undergo central involution

is lacking in some cases, so that the eruption may consist of solid reddish scurfy oval patches. Concentric rings of activity are common. The lesions range in number from a few to a dozen or more. Itching or burning of slight degree may be present, but symptoms are seldom prominent. *The sites of predilection* are the uncovered surfaces. Palms are sometimes attacked and tinea often affects soles and interdigital skin, fingers and hands being involved secondarily. Mucous membranes escape. Perianal skin is often involved and tinea constitutes *one cause of pruritus ani. Mycotic vulvovaginitis is usually monilial.*

Diagnostic differentiation from pityriasis rosea, seborrheic dermatitis, and psoriasis rests on demonstration of fungi in scrapings and cultures. In pityriasis rosea *the eruption is usually confined to the trunk and commonly* begins with the appearance of a herald spot; the lesions are numerous, develop quickly and pursue a relatively rapid course. In seborrheic dermatitis the sternal and interscapular regions generally are affected after the scalp, and



Fig. 618.—Tinea imbricata, Fiji case. (Dr. Harry M. Robinson, Jr.)

the lesions while often circinate are usually irregular. The scales are unctuous, and vesicles are not present except when secondary infection exists. The lesions in psoriasis at times are annular, but they are usually dry and never acutely inflammatory; on scraping off the superficial scales the typical bleeding points are exposed, and the extensor distribution of the eruption is more or less characteristic. See also Infectious eczematoid dermatitis.

Local deep tineal infection may be mistaken for carbuncle, from which it differs in being less acute and far less painful. Diagnosis should be positive by demonstration of fungi, rather than being made by exclusion.

Tender age does not exclude the possibility of mycotic infection. Cases of tinea due to *M. canis, M. gypseum, E. floccosum* and *T. rubrum* occurring in children ranging from 3 weeks to 12 months of age were reported and reviewed by King et al. (ADS 68: 664, 1953).

Tinea Imbricata (Tokelau Ringworm) is a variety of tinea corporis seen in warm, moist climates, due to various fungi of the genus *Endodermophyton*. Infection with *E. concentricum* is characterized by the widespread occurrence of scaly patches which often assume a concentric arrangement. The eruption may become universal and capable of being mistaken for ichthyosis. The

face scalp palms, soles and nails usually escape The health is unaffected Chronicity of the disease is notable It responds only stubbornly even to appropriate treatment and relapses are common. Castellani s fuchsin paint is fairly satisfactory Chrysarobin ointment may be useful.

See Castellani (BJD 25; 377 1913; JTropM 37 263, 1934) McCarthy (J 123: 449, 1943) Gomes (ADS 53 242, 1946); Sharville (BJD 64: 373 1952) *T concentricum* and *T rubrum* in same lesions; Poland (BJD 64: 378, 1952) wide distribution in Malaya

Tinea Cruris (Eczema Marginatum) —Tinea in the region of the groin is a clinical variety of dermatomycosis which may occur also in the axillae or beneath pendulous breasts. It is usually due to *Epidermophyton floccosum* (Wende and Collins ADS 3 1, 1921) but any of several species of fungi may infect these regions. Clinical distinctions independent of cultural identification are unsure I often find *T purpureum*

The infection at first may resemble intertrigo, that is, monilial or streptococcic dermatitis but usually the primary eruption consists of a few superficial, circinate patches which sooner or later coalesce to form confluent symmetric batwing-shaped inflammatory areas which have sharply defined, elevated borders. The margins may be straight, but usually they present a festooned appearance with more or less infiltration. The patches are generally located on the inner surfaces of the thighs, contiguous with the scrotum or labia and the intergluteal regions. In women the mucosa of the vulva is sometimes involved. In either sex the umbilical region may be affected

Extensions along the sagittal line anteriorly and posteriorly give rise respectively to involvement of the mons veneris and the perianal region and intergluteal fold. About the anus and over the coccyx fissuring is particularly likely to occur and distressing and chronic pruritus results. Marginal activity with central clearing and peripheral extension is the conspicuous feature when the lesions extend widely over the thighs and buttocks, and concentric circles of active disease are sometimes seen, as in tinea corporis.

The lesions of tinea cruris are usually moist at first, and they readily become macerated, secondarily infected and painful as well as merely itchy As they heal they become dry scaly and less edematous. Recurrences are common, for the eradication of all fungi is almost impossible while friction, sweating warm weather tight clothing and obesity combine to favor luxuriation of the organism

Tinea of the pedal interdigital spaces and of the nails commonly serves as the source of reinfection, and the feet, usually requiring treatment, must always be examined in cases of tinea cruris. Crural dermatomycosis due to Blastomyces is vegetative and papillomatous in contrast with the macular disease produced by the ordinary organisms of tinea

Tinea of the crotch may be confused with contact dermatitis, seborrheic dermatitis or erythrasma. The location and character of the eruption, its history and the presence of satellite lesions serve for recognition. In monilial vulvovaginitis, shallow pustules and mycotic dermatitis of the near by regions are likely to be present. Tinea of the crotch in women calls for an examination of the vaginal secretions. In erythrasma the patches are superficial and only slightly inflammatory and the causative organism *Actinomyces minutissimus* is readily differentiated by examination of scrapings from *Epidermophyton inguinale*

Tinea of the Hands and Feet.—*Epidermophyton Trichophyton Candida albicans* and other organisms are active here. Tinea of the hands often depends on the existence of tinea of the feet or nails. Dermatophytids of the hands are more common than actually demonstrable tineal infection, and many a case of tinealike pompholyx can be cured by applying treatment to the feet or to some other focus without particular regard to the hands. Streptococcic and staphylococcic dermatitis of the hands, recalcitrant perhaps because of focal infection, is likely to be the correct diagnosis when the hands alone are painfully inflamed in the absence of lesions of the feet (Mitchell: ADS 5 174 1922; 10: 659 1929 J 140 541 1951) The differentiation between mycotic

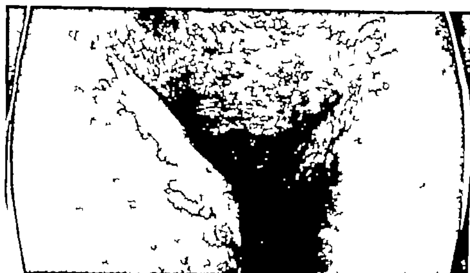


Fig. 619.—Tinea cruris (moniliasis). (Dr. George Miller MacKee.)



Fig. 620.—Tinea cruris "eczema marginatum."



Fig. 621.—Tinea of the crotch often extends to the gluteal region.



Fig. 422.—Tinea of the hand. (Dr George Miller MacKee.)



Fig. 423.—Tinea of the feet, macerated and malodorous, secondarily infected with staphylococci.





Figs. 424 and 425.—Tinea of the feet. (Dr Grover Wende.)

and coccic infections of the extremities is important, for the treatment of the one is not effective for the other

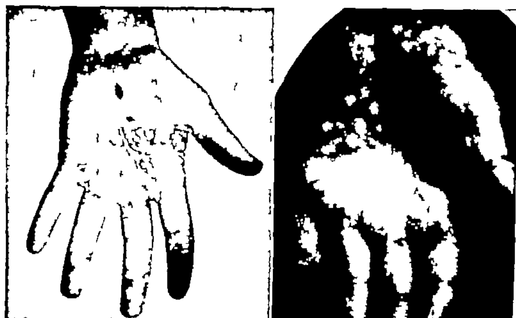


Fig. 426—Tinea of the volar skin. (Dr Fred Weidman.)
Fig. 427—Dermatophytid, vesicular due to active tinea of the feet.

Three principal varieties of cases are seen (White JCutD 37 501 794 1919 ADS 15 387 1927)

VESICULAR, in which the lesions are grouped and are accompanied by marked itching being characterized by sago-grain vesicles and occurring preferentially in warm humid weather;

SQUAMOUS, resembling scaling dyshidrosis, usually with a central primary lesion which results from the drying of confluent vesicles; and

PYOGENIC, resulting from secondary infection.

The essential lesions are usually vesicles, and these may be solitary or multiple grouped or widely scattered. The vesicle is deeply seated only slightly elevated, and has the appearance of a boiled sago grain embedded in the epidermis. Its content is usually clear and as a rule there is no erythema surrounding new vesicles. Within a few days the fluid is absorbed, leaving a brownish macule. Eventually the roof of the dried vesicle becomes torn, exposing a red smooth, shiny surface with a collarette of upturned scales. In acute cases the vesicles may be grouped and may become confluent even forming bullae In extensive acute bullous infections the patient is incapacitated (Ormsby and Mitchell J 67 711 1916) When vesicles are grouped *in a dry area such as the palm or sole desquamation occurs, leaving a circular* well-defined, shiny reddish area denuded of its corneum. This may heal spontaneously or new vesicles may continue to develop about the periphery and extension may occur in all directions. Groups of vesicles may appear in a dry or moist well-defined eczematous area.

The areas affected in their order of frequency are (1) the fourth interdigital space of the foot (2) the plantar surface of the arch, and (3) over the tuberosity of the fifth metatarsal. At the base of the fifth toe a fissure partly interdigital and partly plantar is commonly present Similar fissures may occur beneath all the flexural folds of the toes. Maceration of the exfoliated epidermis in the fourth interspace produces a white sodden thickened adherent mass of epithelium

Hyperhidrosis is usually an associated symptom The patient s complaint is of itching which may be moderate or severe Sensitiveness, *pain and in-*

capacitation occur in acute bullous cases, especially when pathogenic cocci add their effects to the situation.



Figs. 628 and 629.—Not all dermatitis of the feet is tinea. Fig 628 is a secondary syphilid. Fig. 629 is pustular psoriasis. (Dr Royal M. Montgomery)



Figs. 630 631 and 632.—*Trichophyton purpureum* infection of the soles, toenails and finger nails. (Drs. George M. Lewis, Mary Hopper and Royal Montgomery)

Trichophyton mentagrophytes infection in its early stage is acutely inflammatory with vesiculation; and scaling maceration and fissuring may proceed between the toes for months or years, noted Montgomery and Casper (J 128 77 1945 NYSJM 46 2038 1946) who were interested in distinguishing the clinical appearances of the diseases produced by specific fungi Ves-

icles deeply located, filled with viscid fluid and surrounded by not much erythema, characterize this type as it appears on the soles and sides of the feet. The vesicles may become pustular and then dry, become scaly and clear centrally, while vesicles perhaps recur in the central part of the lesions. As these dry there evolve brownish macules that desquamate. The domes of the ves-



Figs. 433 and 434.—Tinea nigra in a young woman, and *C. werneckii* on direct examination. (Carrión, ADS 61: 996, 1950.)

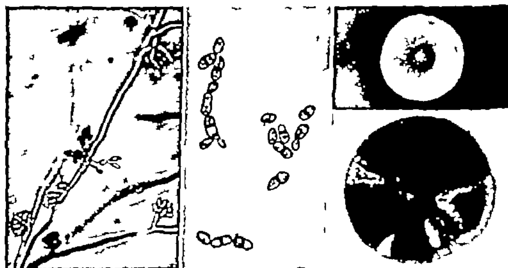


Fig. 435.—*C. werneckii* in hanging-drop culture in 4% glucose broth, showing yeastlike growth. (Dr. A. Carrión.)

Fig. 436.—*C. werneckii* in corn-meal agar slide culture, showing hormodendrum type of porulation. (Dr. A. Carrión.)

Figs. 437 and 438.—*C. werneckii*, moldy giants. Fig. 437 (above) shows 3 weeks growth in 4% glucose agar. Fig. 438 (below) shows 4 weeks growth. (Dr. A. Carrión.)

icles contain easily demonstrable fungi. Infection of the nail plate is usually superficial, manifested by scaling or *small irregular white areas*. *Trichophyton purpureum* produces a noninflammatory dermatophytosis characterized by fine branny scaling and an absence of vesiculation. *In nail infections* this *fungus invades* the under portion of the nail, causing yellow undermined

areas, and the nail plate may be broken off or destroyed. *Candida albicans* infections of the feet are characterized by red and macerated areas usually involving all the interdigital webs. Nails show a paronychia and swelling with the lateral borders of the nail plate ridged and undermined. *Epidermophyton floccosum* infection of the feet causes maceration and severe scaling on the toe webs and flaky scales on the sole but nail infections are seldom due to this organism. Weidman and Glass (ADS 53 213 1946) did not consider *T purpureum* infections especially characteristic finding this organism in many cases with hyperkeratotic and macerated lesions. See *Trichophyton purpureum* infection (p 509)

Inguinal lymphadenitis occurs in many severe and acute cases involving the feet. *Trichophyton interdigitale* has been secured by culture from a swollen inguinal node, the same organism being recovered from the focus (White ADS 18 271 1928) Epstein (ADS 45 1113 1942) demonstrated that some cases of so-called dermatophytids of the hands are actually dermatomycosis, wherein one can find the organisms and obtain cure with parasiticidal medication. Regional lymphadenopathy is usual in kerion but it does not imply the presence of pathogenic bacteria or the need for penicillin injections.

Tinea of the palms and soles is to be distinguished from contact dermatitis, which is ordinarily not interdigital is manifest as severely pruritic patches with fading ill-defined margins, and is most intensely vesicular if vesicular at all, in the central part of the inflamed areas rather than at the periphery Impetigo and infectious eczematoid dermatitis are acutely inflammatory are interdigitally located when they complicate contact dermatitis or scabies, and spread rapidly with vesicles which are not multilocular Streptococcic or staphylococci dermatitis often begins from a specific and remembered minor injury upon which salves have been applied to the therapeutic detriment rather than betterment of the lesion. Coccic dermatitis is more painful and more speedy in its progress than mycotic dermatitis. It is, of course often secondary to tinea, but it must be treated first before fungicidal medicines are to be applied. Oozing, undermining, rapidly spreading tinealike dermatitis involving the dorsum of the feet or involving the hands and not the feet is usually coccic. Fungus infection of asymptomatic character often spreads swiftly and increases in virulence when eczematous dermatitis occurs. Mycologic studies are necessary for positive diagnosis (Mitchell: J 146 541 1951)

Tinea Albigena is an affection of palms and soles especially and rarely of the nails, arms and legs, seen in Java. Nieuwenhuis (AfDuS 89: 1 1908) described the disease with initial vesicles, the skin later becoming hyperkeratotic and fissured. Vitiliginoid depigmentation follows. The causative organism was originally classed as *Trichophyton albiciscans* but Brumpt concluded it belongs to the genus Glenosporella. The disease is said to be responsive to fungicides such as mercuric chloride, iodine or chrysarobin.

Tinea Nigra is a tropical chromophytosis characterized by the development of dark macules, usually on the palms and volar skin of the fingers, according to Carrión (ADS 61: 996, 1950) It was first described under the name Keratomycosis nigricans palmaris by Cerqueira Pinto of Brazil in 1916. The lesions range in color from black to gray some of them resembling the stains of silver nitrate, and are rounded macules of various sizes, sometimes slightly elevated and occasionally scaly They may be discrete or confluent and numerous or sparse The disease is not extremely rare cases having been reported from Asia, Java, Brazil, Cuba and the United States. See McCarthy (J 123 449 1963); Leland (ADS 61: 854 1950)

The infecting organism, *Cladosporium werneckii*, is constantly present in epidermal scrapings from the lesions, from which it is readily cultivated on standard mycologic mediums. The colonies are slow growing, black in color with centers that become raised and furry (Walsh: ADS 57: 722, 1945) Cases affecting the neck and upper thorax were noted by Neves and Costa (ADS 55 67 1947) The disease is asymptomatic and is presumably transmitted by direct contact. It responds readily to treatment with such fungicides as 3% alcoholic solution of salicylic acid, or an ointment containing benzoic acid, resorcinol and sulfur, of each 10%, according to Silva (AmdeD 6 923, 1935) Whitfield's ointment with 5% sulfur added to it promptly cured a case of mine.

Tinea of the Nails.—*Trichophyton gypseum* and *T purpureum* as well as *Candida albicans* and the organism of favus, are the parasites which commonly attack the nails (Rockwood: ADS 22 395 1930) Various aspergilli and other saprophytes are often cultivated too *M canis* is occasionally found in and about the nails (Lyons ADS 67 460 1953) These fungi are capable of living in the nail substance which they invade more or less deeply—*Trichophyton purpureum* attacks especially deeply (Montgomery and Casper NYS JM 46 2038 1946)—and so they cause the nail to become thickened, lusterless, friable and whitish or yellowish in color Progress of invasion toward the nail root exceeds the rate of nail growth so that eventually the entire nail plate may be supplanted by a scaling and horny malformed, infected mass.

The surface layers of the nail plate may be preserved while soggy stinking material accumulates beneath it or *the plate may exfoliate* as far proximally as the invasion of its deeper layers has progressed. Nails may be involved primarily or secondarily to cutaneous infection. Chronic interdigital tinea of the feet eventuates in infection of the nails almost invariably. When the nails have become infected they serve as foci responsible for the dissemination of parasites and for repetitions of ids (Williams ADS 18 730 1928)



Fig. 639 —Tinea of nails leukonychia trichophytica.



Fig. 640.—Tinea of the toenails and skin, clinically suggestive of T mentagrophytes infection (Dr J Lamar Calloway)



Fig 641 —Tinea of nails, clinically suggestive of T purpureum infection. (Dr J Lamar Calloway)

Invasion of the nail is gradual The free extremity of the nail, particularly at the side first is involved. Several nails may be infected, but the dates of onset are separate Sharply demarcated patches of opacity on and within the nail substance, asbestoslike and angulated in outline are known as *Leukonychia trichophytica* (Jessner AfDuS 141 1 1922 Sulzberger and Lewis MRec 146 305 1937) There may be no inflammatory paronychial disease. The organisms are on and within the nail plate and are readily demonstrable

In 2,764 cases of dermatomycosis, White (UOutRev 40: 562 1936) found the nails alone to be involved in 74 cases, and nails and skin in 346. The 3 main types were those d e to trichophytons, monilia and favus. Differential diagnosis was described: psoriasis produced punctate stipling, subungual undermining and partial destruction of the nail plate; avitaminosis produced transverse depressions and longitudinal striae and was benefited by vitamin therapy; and dermatitis of the terminal phalanges due to contactants, cocci verrucae or syphilis wa productive of secondary changes in the nail.

Histologic studies of mycotic nails were made by Alkiewicz (ADS 59: 395, 1949) and Sagher (JID 11: 337 1948) illustrating the fungi spreading within the plate at various levels. The white lines in the nail seen clinically correspond to air filled tunnels due to the invasion.

M. canis infection of the nail and digits is rare but perhaps not so rare as is indicated by the existence of a solitary report by L on (ADS 67 400, 1933) I identified 5 cases i 1949-1951 and, exhibiti g patients, reported on them at the February 193_ meeting of the Kansas City Dermatological Society In 4 cases the fingers and/or fingernails w re affected and in 1 there were lesions on the dorsa of the feet. Both staphylococci and streptococci secondarily infected 3 of the 5 patients in all of whom the disease wa chronic, extremel pruritic and recalcitrant to treatment. Episodes of vesiculation a d exudation occurred in ll of them, but when bateria were from time to time eliminated, the skin lesions were shallow circumscribed patches of dry, itchy dermatitis, more or less excoriated. One patient was a girl of L years, whose scalp was unaffected. Nails were infected in 3 of the 5 patients, and resembled *T purpureum* onychomycosis. While such cases appear to have epidemiologic significance I was unable to trace transmissions of infection. The patient with lesions f the glabrous skin of the feet wa cured but the others were not, despite the use of débridement various fungicides and x ray therapy One patient had radiodermatitis of the fingers, diseased for 1 years before I saw him.

See Kittredge (ADS 34 398, 1936) trichophytosis of all nails Bereston and Keil (ADS 44: 420, 1941) yellow onychomycosis due to *Aspergillus flavus*, Bereston and Waring (ADS 52 162, 1945) case showing *A* *ni* lans and *T rubrum* mixed infection Hem (ADS 54 182, 1946) cases pparently due to *A. glaucus* nd *A* *nid lans*, Moore and Weiss (JID 11 215, 1948) case due to *A. terreus* Kligman (JID 14: 67 1950) case due to a Basidiomycete, a ray fungus generally found on dead wood.

Mycotic Paronychia.—The paronychial tissues are susceptible to fungus infection, although many a rebellious paronychia is bacterial and dependent upon focal infection. The disease may be acute, subacute or chronic. Inflammation, maceration, vesiculation, and fissuring between and about the digits are frequently concomitant The disease tends to be an occupational one affecting individuals exposed to pathogenic fungi while their hands are wet at work (Kingery and Thienes ADS 11 186 1925) Manicuring may serve to inoculate the infection (Oláh DWehn 101 1035 1935) *Candida albicans* is the usual cause (Rockwood: NEngJM 209 295 1933) A Mucor infected orange workers in California according to Sutherland-Campbell and Plunkett (ADS 30 651 1934) Pustular cases accompanied by onychomycosis were ascribed to various organisms by Dósa (DWehn 102 582, 1936)

In the treatment of paronychia, cultures for both bacteria and fungi are helpful to the clinician in selecting appropriate medication. Prolonged exposure to moisture and maceration must be avoided The occasional application of 3% chrysarobin in chloroform is effective A paste of sodium perborate in water was recommended by Rockwood Soaks in $KMnO_4$ may help Gentian violet has been used beneficially X ray treatment 100 r weekly for a few doses, might be given. The elimination of focal infection and appropriate antibacterial measures are often curative

Trichomycosis (Tinea of the Hair)—Fungi parasitizing hair include microspora and trichophytons. Microsporum infections are described under Tinea Capitis. Trichophyton infections were long classified as endothrix and ectothrix, indicating predilection of the fungi for forming spores, respectively within the hair shaft or on it.

Endothrix parasites of importance are *T violaceum* *T sulfureum*, and *T crateriforme* (Levin and Behrman J 128 350 1945) These parasites cause black dot ringworm so called because infected hairs usually without fluorescence split off close to the scalp in scattered patches. The endothrix fungi provoke usually a clinical picture characterized by follicular pustules and small eczematoid patches. Wood s light may reveal dull white fluorescence exceptionally a bright white fluorescence confined to individual hairs and so distinguishable from the glisten of medication which is widely dispersed and can be wiped off with carbon tetrachloride. The KOH preparation shows large spores usually in chains throughout the hair shaft.

Ectothrix parasites are uncommon invaders of the scalp The two im portant ones are *T gypseum* and *T purpureum* The former usually produces pustular inflammation and kerion. Wood s light reveals no abnormality of fluorescence. The microscope shows chains of spores external to the hair shaft. Clinical resemblance to *M lanosum* infection is close but the lack of fluorescence should arouse suspicion Diagnosis requires cultural identifica



Fig 442—Tinea capitis (Dr George Miller MacKee.)



Fig. 443.—Kerion.



Fig 444—Tinea of the scalp fter roentgen epilation. (Dr George Miller Ma k)

tion. *T purpureum* rarely involves the scalp in North America yet it is the organism oftenest found in tinea of the scalp in adults in Peiping (Mu and Kurotchkin ChinMJ 55: 201 1939) Lesions due to it are likely to result in cicatricial alopecia.

Tinea Capitis in Children is a commonplace disease The earliest lesion is a small, rounded, scaly patch or a red papule perforated by a hair The dermis is somewhat hyperemic but the surface is scaly and whitish or grayish in color As the patch slowly widens, it shows no tendency to undergo central involution. Hair shafts become dry lusterless, whitish and brittle They break off and so occasion one variety of symptomatic alopecia. The patches range in size up to several centimeters in diameter and they may coalesce Itching is the principal symptom, and scratching may lead to secondary infection. Tinea capitis in children is an infectious, often seriously epidemic disease of consequence to economy and education It is transferred by barbers, the initial infection in the site cut by clippers, as well as by immediate contact from child to child (Schwartz et al. J 132 58 1946) Children are susceptible to infection while most adults are not. Extract from children s hair was more favorable as a culture medium than from adults reported Kingery et al. (ADS 40: 879 1939) and Rothman et al (Sci 104: 201 1946; JID 8 81 1947) showed that this is due to a relatively high concentration of fungistatic free fatty acids of 5 7 9 11 and 13 carbon atoms in adults hair The fat of adult hair containing normal aliphatic monobasic acids with an odd number of carbon atoms, does not kill fungus spores in hair but prevents their infecting new hairs which replace infected ones in the process of shedding (Rothman et al JID 8 81 1947)

Microsporum canis produces well-defined patches of alopecia, relatively frequently with marked inflammatory reaction, consisting of erythema scaling pustulation and crusting and this may lead to spontaneous cure It commonly produces lesions distinguishable from those of *M audouini* only by cultures.

Microsporum audouini infection is generally not inflammatory but produces gray scaly patches and is not readily curable *M audouini* infections are in fact so resistant that roentgen epilation is usually but not always, required while in other types of infection local applications alone are likely to suffice. The patient of Bereston and Robinson (ADS 68 682, 1953) was only 4 weeks old.

Diagnostically typical are the partly bald, well-defined, scaly areas marked by lusterless and brittle or broken hairs and dilated or débris-stuffed follicular orifices. Microsporum infected hairs are regularly brightly fluorescent although *M gypseum* cases are not (Wilson and Plunkett JID 16 19 1951) One must distinguish seborrheic dermatitis, contact dermatitis, infectious eczematoid dermatitis and alopecia areata. In alopecia areata infected hairs are absent, the bald region is in no way inflamed, and the circular patch of bald scalp is not scaly Compare Trichotillomania.

M audouini caused circinate and imbricated lesions of the vulva and near by skin of a girl 17 years old whose young brother previously was found to have this organism in an ordinary scalp lesion (Silverberg and Oseroff: ADS 69 245 1954 p 498)

Microscopic and cultural examinations are required to distinguish tinea from other diseases as well as to distinguish one kind of tinea from another, and this is of great practical importance. A broken whitish stub is extracted with an epilating forceps. It is placed in a drop of 10% potassium hydroxide solution on a glass slide and after a few minutes it is examined under the microscope. Fungi are ordinarily easy to find if they are present and a fruitless careful search is one criterion of cure

The organisms found in 288 Connecticut cases by Swartz et al. (ADS 60 486, 1949) were: *M canis* in 63% *M audouini* in 25% and *T schoenleini* in 8%; and there were occasional cases showing *M fulvum* *T mentagrophytes* and *T sulfureum*. While *M. audouini*

affected 3 times as many males as *females*, the incidence of *M canis* was equal in the sexes. X ray epilation proved necessary in 23% of the 283 cases. Of these epilations, 54% were performed because of *M audouini* infections and 3 % because of *M canis*.

Cultures from 170 cases in San Antonio by Lehmann et al. (ADS 61 483 1950) showed Microsporum in 68% (90 cases of *M canis* 10 of *M audouini* and 6 of *M fulvum* infection) and Trichophyton in 35% (23 cases of *T mentagrophytes* 18 of *T tonsurans* and 4 of *T violaceum* infection) and several were unidentified.

While clinical distinction between *M canis* and *M audouini* infections is not sure, suggestive differences were listed by Beare and Cheeseman (BJD 63 165 1951)

On a map showing the geographic distribution of cases, those due to *M canis* occurred haphazardly while *M audouini* cases occurred in localized areas. *Inflammatory reactions* were more common with *M canis*. Early *M canis* infections showed brilliant fluorescence but often lost this brilliance in a few weeks, while *M audouini* infections never diminished in the brilliance of their fluorescence If long hairs fluorescent throughout their length were present in an infection of short duration, the fungus was probably *M. canis*. Tinea corporis accompanied tinea capitis far more frequently with *M canis*. From three-fourths of the *M canis* infections a history was obtained of the presence in the household of a kitten having skin disease. Some *M audouini* infections cleared spontaneously and in those that did, there occurred early in the infection fluorescence of the distal two-thirds of the intrafollicular portion of the hair shaft which broke so as to produce partial alopecia, following which the hairs grew out fluorescent even to a length of 2 inches, while the number of infected hairs in the area decreased, fluorescence diminished and spontaneous cure ensued.

See Lewis and Hill (ADS 29 890, 1934), *M canis* and *M audouini* Lewis (AmJMedSci 189 364 1935), animal microsporons Smith (SouthMJ 28 610, 1935) microsporia Lewis and Hopper (ADS 35 461 36 821 1194, 1937), *M audouini* infection harder to cure than *M canis*, Moore and Conrad (ADS 42 610 1940), *M gypseum* case, Benedek and Felsher (ADS 49 120 1944) 140 Chicago cases, 81% *M audouini*, 12% *M canis*, not clinically distinguishable, Wilson and Plunkett (AnnWestMAS 1 93, 1947) review Montgomery et al. (NYSJM 46 679 1946), 2,457 N Y Skin and Cancer cases, 81% *M audouini*, Kinnear and Rogers (BMJ 2 854, 1948) Scottish statistics and epidemics Robinson (ADS 5 391, 1948) iodine, phenol and ammoniated mercury are as good as any antiseptics tested in vitro against *M audouini*, Franks and Mandel (ADS 62 54 1950), 3 members of one family including 2 adults with *M audouini* infection of scalp, Lewis (ADS 63 277 1951) *T craterriforme* kerion in child, Moore et al (ADS 66 382 1952) *T rubrum* ectothrix, produced scarring, Georg (PHRpts 67 53, 1952), *T tonsurans* health problem Bereston and Cohen (ADS 70 817 1954), quinacrine given for discoid L. E. induced green fluorescence of scalp hair Beare and Walker (BJD 67 101 1955) nonfluorescent *M audouini* and *M canis* scalp infections, exceptional, 3 cases.

Epidemic Tinea Capitis.—By 1943 reports from New York, Philadelphia and Pittsburgh indicated to the U S Public Health Service that an epidemic existed in this country and it spread during the subsequent 5 years for the most part fading out by 1949 See Lewis et al. (NYSJM 44 1327, 1944) In 1944 Hagerstown, Maryland requested assistance in controlling the epidemic which had come to involve about 600 of the 7 000 grade school children 98% of the cases being due to *M audouini* (Schwartz NYSJM 47 1782, 1947)

The control of this epidemic was described by Schwartz et al. (PubHBull #294 U S Govt.Printing Off 1946) the plan being based on the knowledge that the parasite is spread by contact with infected hairs and that the principal places of contact are in the home, in school on the playground, in motion picture theaters and in barber shops. Infected hairs were frequently found in the electric clippers of barber shops. All school children were surveyed with Wood s light at 3-month intervals, and preschool children in families with infected children were also examined. Strict quarantine could not be enforced so infected children were allowed to attend school provided they would wear closely fitting caps. Treatment centers were set up with trained personnel in 7 of the schools, and treatment was accomplished with topical medication and manual epilation after initially clipping the hair close Treatment was administered by the trained personnel. The 2 most effective fungicides of the many tried were (1) 5% salicylanilide in Carbowax 1,500 and (2) saturated solution of copper undecylenate in Carbowax. Of the 312 children cured, out of 403 treated about half were cured within 4 months, while 11% were treated for 10 months or longer

The Hagerstown experience is a model of Public Health Service assistance in such circumstances. Lee (PHRpts 63 261 1948) reviewing the problem stated that control requires early diagnosis and adequate treatment of every case. The disease should be reportable and treatment by qualified der

matologists should be made available In the Minnesota experience of Steves and Lynch (J 133: 306 1947) involving about 850 children, only 25% could be cured by manual therapy whereas 80% of those receiving roentgen epilation were cured. Of 208 patients epilated, 207 were cured by Carslaw (BJD 63 16 1951) who felt that fungicides are not necessary in adjunct to roentgen treatment.

EXPERIMENTAL INOCULATIONS of hairy scalp and glabrous skin in children and adults with *M audoui i* and *M ca is* were made by Kligman (JID 18: 231 195_; AD 71: 313, 1955) When infected hairs were rubbed onto the scalp with not too much trauma, takes occurred in about half the cases. On about the sixth day a narrow band of fluorescence developed in the newly infected hair some 0 75 mm. distal to it papilla, and this band lengthened as the hair grew out, reaching the follicular orifice about the thirteenth day Prior to this, by about the tenth day the hair could not be manually epilated because it broke off. Fungus did not invade dead hai It branched as it grew proximad toward the root of the live hair and by the twelfth day reached the cells of the keratogenous region forming Adamson's fringe but not growing i to the nucleated cells. If the hair was manually epilated, it broke off at Adamson s fringe leaving fungi in the intrafollicular st mp. Hyphae spread in the corneum during the stage of peripheral extension of infection, and tinea spreads on the scalp a it does on the glabrous skin. As it spreads on the scalp, the infection of hairs is incidental. The circular hape of the scalp lesion is secondary to the peripheral spread of hyphal invasion f the corneum, b t hyphae ca not be found in the corneum after the lesion has reached its maximum size, which takes about 3 months. At the periphery of a spreadi g lesion, newly infected hairs show a band of fluorescence proximally located. The detection of such hairs demonstrates that a lesion is in fact a spreading one for they do not occur at the periphery of lesions which are not spreading They are not found in a case which has become stabilized and in which new lesions will not develop. When hairs with banded fluorescence are found, the disease may be interpreted as of recent origin, less than 3 months in duration. After that time some sort of refractoriness apparently develops in the patient, but no explanation is known for this. Stabilization suggests that one might perform a local epilation, but this does not in experie ce turn out well. Local epilation should never be done.

Microsporum gypseum (fulvum) generally produces nonfluorescent inflammatory scalp infections. Of the 9 cases reported on by Dalton et al. (JID 15 421 1950) 6 affected the scalp and 3 the glabrous skin. All patients but 1 were children, all scalp cases were of the kerion type and these all resulted in atrophic depressed scarring The organism was an ectothrix. Its colonies on Sabouraud s dextrose agar were cinnamon in color flat and without radial or concentric furrows. The growth was suedelike with a white, powdery margin. On microscopic examination numerous microconidia were seen. The extremities of the fuseaux were rounded, the walls thin, and the transverse septations usually 4 in number

Wilson and Plunkett (JID 16 19 1951) too commented on the absence of fluorescence in their 7 cases, although fluorescence has been thought typical of other microsporum infections. *M gypseum* infections of the scalp are somewhat uncommon, but cause as a rule large boggy, crusted, sore kerions in children, which heal spontaneously after 2 or 3 months, little influenced by treatment unless perhaps an epilating dose of x ray therapy hastens involution. Cases have been noted by Sharp and Wegner (ADS 61 824, 1950) and Trice and Shafer (ADS 64 309 1951) Cawley and Grekin (ADS 60 435, 1949) reported a favoid lesion of the scrotum due to this organism On the glabrous skin, the lesions are usually inflammatory but cannot be distinguished clinically from other forms of tinea corporis. I identified 5 cases from Missouri and Kansas in the years 1930-1933 Brazilian cases were reported by Gonçalves (YBD 1953 p 209) Rare in Great Britain, the infection was observed as an epidemic involving 8 of 40 greenhouse employees by Whittle (BJD 66 353 1954) The lesions were annular and erythematous, with thick walled vesicles at the edges, and they were cured by applications of iodine and occlusive covering after about 5 weeks of treatment

M gypseum has a world wide distribution It has been isolated from soil samples in numerous localities by Ajello (JID 21 157 1953) to whom it appeared as a soil inhabiting fungus only occasionally parasitizing animals. It seems to participate in the microbiologic breakdown of keratin, for it is found by offering hair for it to thrive upon, the filaments becoming covered with a

yellowish white mantle of mycelium and penetrated to various depths by interesting perforating organs. The organism was found in soil samples from Cuba and was proved pathogenic in man and cat by Fuentes et al. (AD 71 684 1955)

Epidermophyton inguinale was found in a case of pityriasis of the scalp by Gjessing and Mossige (ADS 36 1154 1937)

T discoides (faviforme) is a fairly common cause of tinea capitis in England (Beare BMJ 1 356 1954) It was the cause of 3 cases of kerion in 1 family reported by Saunders (ADS 69 365 1954) See Kerion.

Tinea Capitis in Adults has been thought to be quite rare in Europe and America but common in Japan. It affects women more often than men and is usually of the noninflammatory type although kerions are occasionally reported (Cummer ADS 36 844 1937, Benson ADS 39 484, 1939)

Fowlkes and Fox (ADS 11 446 1925) collected 50 cases from the literature and added 3 of their own the majority of the infections being with endothrix trichophytons The elderly female patient of Mendelsohn and Muskatblit (NYSJM 38 803 1938) had *M canis* infection. The patient of Klumpp and Reiss (ADS 56 547 1947) was the mother of 2 children also infected with *M audouini* as was the patient whose scalp was cured by manual epilation and salicylanilide although her infected daughter required x ray epilation, reported by Morgan (JKansMS 50 231 1949) Kligman and Ginsberg (JID 14 345 1950) were not able to find an allegedly superior fungistatic activity of postpubertal sebum as compared with hair fat of children.

The excellent and comprehensive study of Pipkin (ADS 66 9 1952) demonstrated that tinea capitis in adults is not so rare as has been thought, especially in the Southwest, and that the clinical features frequently are diagnostically confusing Scalp disease inflammatory or not must be suspected of being mycotic whether or not fluorescence is evident.

T tonsurans infection of the scalp may be suspected when the involved plaques tend to be angulated or polygonal rather than rounded when the hairs are broken off so close to the scalp as to appear as black dots, and when the infection is unduly prolonged or continues after puberty wrote Howell et al. (ADS 65 194 1952) Fluorescence is almost uniformly absent, the direct examination shows an endothrix invasion and cultures yield the specific growth. On following the clinical course of a particular plaque there are 3 stages of evolution generally to be distinguished, although all stages are likely to be present in any given patient During the epidermal phase there are a few patchy areas resembling seborrheic dermatitis. During the phase of follicular invasion, there are broken hairs and small areas of resultant alopecia which areas are of unusual shape—finger like rectangular or oval with irregular borders—often only 2 or 3 mm in diameter seldom as large as 5 cm Folliculitis is present and, in children, kerion is frequent. The third phase is that of healing, without permanent alopecia

The *T tonsurans* group was responsible for 91% of the endothrix infections, 87% of all trichophyton infections and 73% of all cases of tinea capitis in adults in Pipkin's Texas series The diagnostic clue was the infected stub of the hair a dot speck or imbedded fragment which required careful seeking if it was to be found. Wood light was of no diagnostic help. Epilating x ray therapy was the only attack hopeful of success, and it must be followed by meticulous manual removal of residual infected material.

In the familial epidemic of *T tonsurans* infection described by Kligman and Constant (ADS 63 493, 1951) the endothrix trichophyton produced noninflammatory scalp lesions with fluorescence dull or absent and the trichophytin test remained negative. They cured the cutaneous lesions by x ray epilation and Whitfield's ointment but were unable to cure the nail infection in these patients. The extensive and recalcitrant case affecting an adult female observed by Cipollaro (ADS 68 226 1953) spread from the scalp onto the arms and hand Of 44 New York cases collected by Reiss (BJD 66 229 1954) the scalp was involved in 29 and the glabrous skin only in 11. Lesions of the glabrous skin were usually located on the nucha, cheeks or upper chest A forehead case resembled pityriasis streptogenes. Sometimes the lesions resembled chronic lichenoid eczema.



Fig. 645.—Kerion, spontaneously healing, seldom produces so much cicatricial alopecia as is seen here



Fig 646.—Kerion of beard.



Fig. 647.—Kerion of moustache. (Dr Gusta Riehl.)

TINEA CAPITITIS IN ADULTS.—See Fox (ADS 13 398, 1926) *M audoui i* case Levin and Behrman (J 126 360 1916) nonfluorescent tinea capitis, Lewis et al. (J 133 62, 1946) *M audouini*, Felsher and Finnerud (ADS 58 517 1948) *M audouini* 1 mother and children, Reif (ADS 59 662, 1949) *M* *adou* i in pregna t Negroes H rschmann and Olansky (ADS 61 122, 1950), *M audouini* case; Greenhouse (ADS 63 502 1951) *T violaceum* case Weber and Ulrich (ADS 66 624 1952) *T rubrum* case.

Tinea Barbae.—SUPERFICIAL TYPE.—Infection may involve several hair shafts to a greater or lesser extent but seldom to the extent seen in tinea capitis. Infected hairs become dry and brittle and can usually be extracted readily the diseased root-sheath often adherent to the shaft There are more or less infiltration scaling and itching Vesiculation and pustulation are commonly absent. The disease frequently remains superficial throughout its course.

DEEP TYPE.—Deep involvement characterizes many cases, either from the beginning of the attack or after the disease has been present for several days in superficial form. The lesions may be few or many Numerous, dissem inated lesions constitute sycosis as distinguished from kerion, in which the lesions are large carbunculoid and few These inflammatory tumors are flat or oval and reddish and are studded with dead or broken hairs or with gaping follicular orifices. Such nodules may ulcerate in the center but ordinarily pus and seropurulent material are discharged through inflamed, dilated

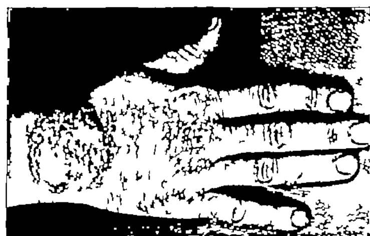


FIG. 441.—Agminat f lliculitis, n infection f animal origin (Dr M. L. Heidingsfeld)

follicular openings. The common site for the lesions is the skin beneath the jaw and in the cervicomaxillary fold. As a rule the upper lip escapes. This inflammatory form of tinea barbae usually exhibits a tendency to undergo self healing

Kerion may be caused by a y of several different f ngi, incl ding *M canis*, *M audouini*, *M fulvum* *T gypseum*, *T niveum* and *T crateriforme* (Birt and Wilt: ADS 69: 441 1954) *T fai forme* caused 1 of 39 cases of Carney (ADS 59 709 1949) and infected a mother and child reported by Muskatblit and Fisher (ADS 63: 723, 1952) *T sulfureum* caused a kerion of a child s scalp reported by Moore and Wool ridge (ADS 61: 460, 1950) A beard lesi n due to *T purpureum* was observed by Loewenthal a d Rein (ADS 63 19 1951) Upper lip lesions were discussed by Davidson and Dowding (ADS 61: 660, 1932) Similarity to bromoderma wa noted by Smith (BJD 50: 333, 1935) Agmi ate follicul tis, kerion, Majocchian granuloma a d tinea circinata were the configuratio of cattl ri g worm observed by Rook and Fra Bell (BMJ 1199 1954) whose cases were predom inantly caused by *T mentagrophytes* and *T discoides* *lbum*, respectively small spore a d large spore ectothrix parasites.

Cultures are best obtained from the pus. After an average duration f from 6 to 8 weeks the hair may be expected to regrow (Laymon MI M 29: 137 1946) and wh le expectant treatment i sufficient, manual epilation may help.

Kerion f the scalp l k keri n of the beard Sim lar carbuncular lesion on the dorsum of the hand or forearm may be called gminate folliculitis. S pporat ve ring worm contracted from cattle wa discussed by Fowle and George (ADS 56 90 194) Tinea barbae due to *Favotrichophyton alb m* was identified by Gammel and Wo k (ADS 33: 756, 1933)



Fig. 449.—Tinea of hair: section showing endothrix invasion of shafts within follicles. (Dr Fred Weidman.)





Figs. 450 and 451.—Fungus infections of hair. KOH preparations. Fig. 450 shows T. mentagrophytes causing ectothrix disease. Fig. 451 shows T. violaceum causing endothrix disease. (Dr Emanuel Muskatblit.)

Suppurative Tinea is a name designed to include kerion, sycosis, and agminate folliculitis. Variants of *Trichophyton gypseum* are the usual offenders. Many such cases occur in people who handle cattle. The trichophytin test is usually positive in suppurative tinea. Fowle and George (ADS 56 780 1947) reported 23 cases contracted from cattle and due to various trichophytons.

Of the 46 cases of suppurative tinea all occurring in farmers or cattle dealers, reported on by Davidson et al (CanadMAJ 31 587 1934) 10 were of kerion 29 of sycosis and 7 of agminate folliculitis, and all developed during the late winter or early spring months. Wood's light examinations were negative but the trichophytin test became positive in all. Immunity evolved slowly but self healing was in evidence for starch and boric poultices were satisfactory treatment.

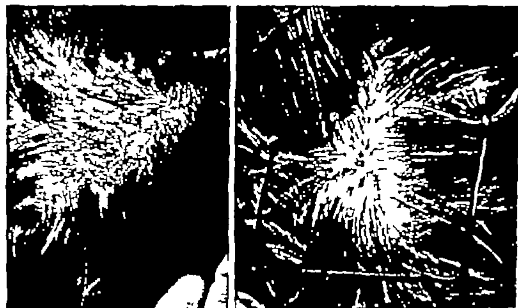


Fig. 652 and 653.—Tinea amiantacea. (Brown BJD 60 31 1948.)

Granuloma Trichophyticum is a type of deep ringworm differing from kerion chiefly in its chronicity and its milder degree of inflammatory intensity. It does not suppurate until late or unless it becomes secondarily infected. It occurs on the scalp and beard in connection with pre-existent fungus infection, and on the dorsa of the hands, forearms, and feet. The lesions are sharply defined and have smooth surfaces. They may persist for months or years. Sometimes they are acutely inflammatory sometimes hard and keloid like with deformed hairs at the periphery. They may occur on the leg and are readily mistaken for erysipelas, lichen chronicus simplex or stasis dermatitis. See *T. purpureum* infection (Wilson et al ADS 69 258 1954)

Tinea of the Eyelashes.—There may occur (1) folliculitis of the lashes and hair of the eyebrows with redness, swelling and perhaps purulent exudation, (2) edema of the lid margins without scaling or (3) scarring followed by loss of lashes noted Weidman (System of Medicine Appleton-Century 10 133 1937). The involvement may be unilateral or bilateral, and a child or an adult may be affected. The usual organisms are *T. sulfureum* or *T. violaceum*. The case of an 8-year-old boy reported by Silvers (ADS 49 436, 1944) was due to *M. audouini* was secondary to a lesion on the cheek showed classic fluorescence and was cured by manual epilation. *M. canis* infections of the lashes are quite rare according to Franks and Mandel (ADS 62 708 1950) who reported a case and reviewed the literature. See Montgomery and Walzer (ADS 46 40 1942) Costa (ADS 48 65 1943) Mitchell and Goodwin (ADS 64 655 1951)

Tinea Amiantacea, asbestos-like tinea, is a scalp disease wherein heavy scales extend onto the hairs, binding together the hair shafts. It may be circumscribed or diffuse. It is chronic It is not followed by atrophy scarring or alopecia (Becker and Muir ADS 20 45 1929) The condition was interpreted as a symptom complex which may occur in neurodermatitis or psoriasis and is responsive to an ointment containing 5% each of salicylic acid and oleate of mercury and to small doses of x ray therapy (Brown BJD 60 81 1948) Brown preferred the name Pityriasis amiantacea, believing that fungi are not causative The favorite prescription of Behrman (The Scalp in Health and Disease, Mosby 1952, p. 390) consisted of salicylic acid 6 ammoniated mercury 3 alcoholic solution of tar 1 water miscible base to 100 Chloramphenicol 0 6% in Vioform Cream is effective.

Piedra is a disease of the hair seen in some districts of South America and elsewhere It is characterized by the development of dark, nodular pinpoint to pinhead-sized, gritty masses on the shafts of the hairs of the scalp eyelashes or beard (McCarthy J 123 449 1943) Known also as

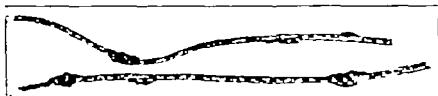


Fig. 411.—Piedra from an Indian girl of British Guiana. (Dr J. M. H. Macleod.)



Fig. 412.—Piedra KOH preparation. ×94. (Dr E. Muskatblit.)

trichosporosis or tinea nodosa, this fungus infection is limited to the shaft of the hair without involvement of the skin. The hard nodules (piedra means stone) adhere to the sides of the shaft like nits or form collars about it. White piedra is seen especially in Colombia, and is due to *Trichosporum beigeli* the spherical cells of which some are 10 µ in diameter and form a dense mat adherent to the hair because of a mucilaginous product of their growth. *Piedraia hortai* produces black piedra, affecting scalp axillae and beard a common and infectious disease of the scalp among Siamese children, according to Kneedler (ADS 39 121, 1939) A North American case was identified by Scott (ADS 64 767 1951) Cultural characters of the causative organisms are given by Moore (Clinical Tropical Medicine Hoeber 1944 p. 652) Shaving the head affords a quick cure but frequent shampoos followed by bichloride rinses or ammoniated mercury ointment will also succeed (Behrman The Scalp in Health and Disease Mosby 1952, p 341) The nodules can be dissolved off the hair with xylene.

Lepothrix (Trichomycosis, which may be yellow black, or red) is a dermatomycosis characterized by the occurrence of colored concretions on, or soft sheaths surrounding the axillary hair Adjacent skin is often infected. Concretions on the hairs are composed of masses and chains of micro-

Figs. 656 and 657.—Nodule of piedra on hair shaft, low and high magnifications. (Originals of Dr. Emanuel Muskatblit, from Behrman: The Scalp in Health and Disease, Mosby, 1952.)

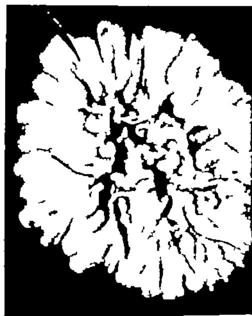




Fig. 658.—Culture of *Trichosporum beigeli*, of white piedra. (Dr. E. Muskatblit, from Behrman: The Scalp in Health and Disease, Mosby, 1952.)

Fig. 659.—Culture of *Piedraia hortai*, of black piedra. (Dr. E. Muskatblit, from Behrman: The Scalp in Health and Disease, Mosby, 1952.)





Fig. 660.—Lepothrix: trichomycosis axillaris nigra. (Dr J Lamar Calloway)
Fig. 661.—Lepothrix: trichomycosis axillaris flava (Dr O G Costa.)

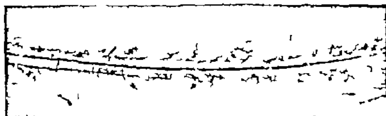


Fig. 662—Lepothrix. (Dr Fred Harris.)

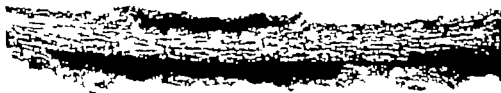


Fig 663.—Lepothrix, KOH preparation, ×120 (Dr E. Muskatblit.)

organisms embedded in a homogeneous, chitinlike substance Species of Actinomyces mingled with certain cocci, have been thought to be the cause (Lane JCutD 27 387 1919)

The yellow type, allegedly due to *Actinomyces tenuis* is the commonest. Also due to *A tenuis* but with red pigment from the concurrent presence of *Micrococcus castellani* clumps of which grow in the gelatinous mass on the hair the red type is less common The black type is least common both in the tropics and in temperate regions, and is due to *A tenuis* and an associated pigment producing bacterium *Micrococcus nigrescens* (Castellani BJD 23 341 1911 25 14 1913) The nodules in the yellow type are homogeneous, soft and gelatinous, and added to them may occur clumps of red or of black cocci so as to produce the other types according to Moore (BJD 50 659 1938 ADS 37 967 1938) See Castellani and Wilkinson (BJD 34 255 1922 JTropM 26 186 1923)

Microbiologic studies by Crissey et al. (JID 19 187 1952) failed to confirm the nocardial nature of the causative organism which they believed to be a peculiar diphtheroid It fermented lactose and dextrose and grew best in an alkaline medium They named it *Corynebacterium tenuis*

The disorder can be cured by shaving the hair and washing the skin with benzine followed by 1 1 000 alcoholic solution of mercuric chloride

Otomycosis and Myringomycosis.—Many fungi are alleged to be capable of provoking inflammation in the skin of the external auditory canal and ear Itching dermatitis and impedance of hearing result On the tympanum parasites may form a coating of mycelium of blotting paper like consistency and bad odor Many different organisms, such as aspergilli generally considered nonpathogenic have been accredited with causing otomycosis. Branny desquamation or moist exfoliation with oozing is seen The truth is that the large majority of cases of dermatitis of the external ear are due to contactants, lichenoid dermatitis and bacteria working singly or in conjunction. Antibacterial therapy is more likely to succeed than fungicides, which often only irritate (Syverton et al AOtol 43 213 1946) *Pseudomonas aeruginosa* is a common offender which neomycin, chloramphenicol or polymyxin may eradicate (see p 327)

Otomycosis and myringomycosis do not undergo spontaneous resolution. They generally respond favorably to mild antiseptics along with careful débridement Recurrence is likely Ten per cent salicylic acid in 70% alcohol may be dropped into the canal Silver nitrate solution may be swabbed over the affected skin Metacresyl acetate has been highly recommended (Whalen J 111 502, 1938) Reeh (AnnOtol 51 146 1942) added 1% thymol. Sodium propionate 8% in propyl alcohol for swabbing twice daily followed by insufflation of 10% sodium propionate in talc was the recommendation of Duemling (ADS 52 75 1945) A wick moist with saturated aqueous solution of boric acid may be kept in the canal.

Rarely nowadays does one make a diagnosis of dermatomycosis of the ear My treatment of such cases many of which are referred by otologists whose fungicidal efforts proved futile or worse includes (1) prohibitions with respect to what may touch this region omitting toilet articles and cosmetics (2) attack upon seborrheic dermatitis of the scalp with Selsun or a lotion such as 1½% phenol 1 2,000 bichloride of mercury and 3% resorcinol in 70% alcohol (3) 2% sulfur and 0 8% Chloromycetin in Vioform Cream swabbed lightly on the dermatitis several times daily without filling up the canal (4) gentle syringing with 1 5,000 KMnO4 and (5) elimination of foci of infection in the stubborn cases. Cortisone by mouth and perhaps hydrocortisone ointment are helpful in cases which are primarily lichen chronicus simplex (q v) in this location

See Chronic Dermatitis of the Ears Dowling and Levey (CanadMAJ 41 336, 1939) Mucor causing obstruction deafness, Simon (WVaMJ 25 482, 1929) importance of treatment Dart AOtol 31 885 1940) Cresatin and thymol Minchew et al. (SouthMJ 33 1312, 1940) Cresatin and thymol Dunn (MJAustral 2 427 1941) carbol-fuchsin and sulf[illegible] powder Gill (SouthMJ 40 637 194[illegible]) Cresatin wick, zinc peroxide Dixon (JMoRMA 44 181 1947) clinical management of ear canal infections Hayes and Hall (AOtol 47 289, 1948) importance of Ps. aeruginosa Stuart (CanadMAJ 7[illegible] 334 1955) aspergillosis, 29 cases.

Trichophyton Purpureum Infection is sufficiently distinctive to be recognized from its clinical manifestations with some assurance (Lewis et al. ADS 37 823 1938) The lesions are likely to be solid, lichenoid plaques spreading at the borders with follicular papules, affecting the hands and feet groin back, thigh or umbilicus. They are superficial pruritic and extremely rebellious. Rarely granulomas are produced by this organism. Undermining and destruction of the nail plate are typical when onychomycosis is the case Hair involvement is exceptional, lesions being scattered follicular pustules and the organism behaving as an ectothrix (see tinea capitis in adults, p 500) Three cases of kerion of the beard due to *T purpureum* were reported by Sawicky et al. (AD 71 641 1955) See Figs. 630-632 In therapy potent topical agents must be used with persistence.

Extreme distribution and resemblance to dermatitis herpetiformis were reported by Tolmach and Schweig (ADS 41 732 1940) Experimental infection of rabbits interested Reiss (ADS 49 242, 1944) Cultural studies were detailed by Lewis and Hopper (ADS 41 893 1940) Swartz and Conant (ADS 42 614 1940) preferred the name *T rubrum*, and recommended inhalations of ethyl iodide in treatment A case of Baer and Muskatblit (ADS 60 445 1949) resembled erythroderma ichthyosiforme improved on Pragmatar eventually developed onychomycosis. The organism has been recovered from deep scrapings of lesions resembling chronic lichenoid eczema of the leg by Wilson (ADS 65 375 1952) see Cremer (Dermatologica 107 28 1953) Most of the patients of Wilson et al. (ADS 69 258 1954) were brunette women 19 to 50 years of age in whom usually solitary lesions assumed the form of chronic dermatitis of irregular outline showing cyanotic erythema, variable scaling and firmly indurated nodules. These were only slightly raised, not painful and only mildly itchy persisting for months but tending to undergo spontaneous regression with resultant circular atrophic scars. In late stages necrosis with ulcerations and crusting but not pustulation, sometimes occurred. Histologically the granulomatous infiltrate contained scattered fungus elements and the hairs showed globular spores externally and chains of round spores and short hyphae within. Wilson et al. obtained cures with sprays of 5% Asterol twice daily inunctions of Asterol ointment, potassium iodide 45 to 60 grains daily by mouth and small doses of x ray therapy

Involvement of the hands is clinically fairly typical, the infection of glabrous skin resulting from onychomycosis. Dry marginate chronic eczema is seen, usually unilateral often largely volar in distribution. Of 39 cases reported by Thompson (SouthMJ 47 130 1954) 30 were unilateral and males were affected 5 times as frequently as females. Thompson had good results with the antifungal preparation of Lyons et al. (USAFMJ 4 1175 1953) although no case of *T purpureum* onychomycosis was cured even by avulsion. The formula of Lyons et al, contained sodium propionate 2.0 sodium caprylate 2.0 propionic acid 3 0 undecylenic acid 5 0, salicylic acid 5 0 copper undecylenate 0 5 dioctyl sodium sulfosuccinate 0.1, water 20 0 propyl alcohol (91%) to make 100 0 The use of this prescription resulted, Lyons et al reported, in cures within a month in 15 of 17 cases, and in those that were not cured, cultures became negative. Lyons (pers. comm., 1955) had not changed his opinion of the value of his preparation (Verdefam Texas Pharmacal Co) after additional favorable experience The few cures I have secured resulted from the vigorous use of chrysarobin in an ointment or in chloroform solution.

A remarkable gyrate, urticarial and erythematous eruption due to *T rubrum* was observed by Waisman (JID 22 237 1954)

In 3 generalized cases of *T rubrum* dermatomycosis, there was coexisting lymphoblastoma, suggesting a relationship of unknown nature, reported Lewis et al. (ADS 67 247 1953)

See Castellani (JTropM 37 368 1934) permanent alopecia (scalp cases seen in Ceylon and China) Oertel (DWchr 102 166 1936) lesions of glabrous skin Morikawa (AfDuS 176: 364, 1937) nodular granulomas Ludwig (ADS 68, 310, 1953) sycosiform tinea barbae Lewis and Spoor (ADS 68 364, 1953) boy with widespread, gyrate, erythematous lesions;

Rothman (ADS 67: 239 1953) recalcitrant olar and nail cases, many of which showed increased glucose tolerance perhaps pertinent t pathogenicity cures of some skin, no nail infections, with concentrated lithium bromide and glucose solution.

Mixed Infections.—It is possible for a single host to harbor 2 or more pathogenic fungi at the same time. Several cases were described by Muskatblit (ADS 44: 631, 1941; 54: 658 1946) in one of which cultures from the foot demonstrated both *T interdigitale* and *T purpureum*. Mixed infections of the scalp interested Loewenthal (ADS 58: 27 1948) who found combinations of *T schoenlei* with *T violaceum* and with other organisms and one case with both *M canis* and *M audouini*. *T gypseum* on the face and *T violaceum* in the nails were present in the patient of Cawley and Horne (ADS 59 66 1949), while *E floccosum* and *T rubrum* were found on the hands and feet of the boy reported on by Franks and Rosenbaum (ADS 62: 439 1950) Four different pathogens were cultivated from the feet of a young man by Wooldridge (ADS 63 633 1951)!

Miscellaneous D ta on S perficial F gus I fections

T mentagrophytes—Dowding and Orr (BJD 49 298, 1937) hands, feet, beard, scalp Georg and Maechling (JID 13 339 1949), mutant with orange pigment from cases affecting skin and nails Franks and Frank (ADS 63 469 1951) case, astonishing erroneous dermatitis of feet.

T sulfureum.—Slaughter and Cawley (JID 9 63, 1947) lesions of child legs with —ld Samman (BJD 63 325, 1951) inveterat case forearms and nails with lichenoid lesions simulating those often due to *T. rubrum* Franks et l. (ADS 65 95, 1952) multipl kerion and erythema nodosum in a child.

A. gypseum. Shaban (ADS 36 335, 1937) caused scaly disease of guinea pigs, not of human beings.

T fluviale.—Szathmáry (ArDuS 181 192, 1940) occurrence in soil nea ri er infecting human beings.

T cameroonense.—Bernhardt (ADS 55 237 194) mycology of case showing itchy red spots.

Microsporum (Trichophyton) ferrugineum.—A common cause of tinea tonsurans in children in Japan, the organism was extensively studied a d so named by Ota (JapJ Dermat 21: 201, 830, 1921; BullSocPath Exot 15: 599 1922) because of the rusty reddish yellow to orange color of its colo ies. Soon Bong S h told me it is the most important causative agent of tinea capiti and tinea corporis in Asia, especially in Japan China and Korea, although *M sapporoense* is a common cause of tinea capiti in Hokkaido. *M. ferrugi eum* has been isolated in Uruguay and central Africa, a d an organism closely resembling it was found in children in India by Maplestone and Dey (I dMedGaz 74: 143, 1939) The clinical picture resembles that produced by *M audou* but the lesions are not fluorescent in Wood s light. Lesions of the glabrous skin are often located on the face where they resemble pityriasis simplex (see Reiss BJD 66: 239 1954) See Brumpt (Précis de parasitologie Masson, 1949 p. 1938); Dodge (Medical Mycology Mosby 1935, p. 545) thought it closely related to *M equinum*

Favus is the dermatosis due to infection with *Trichophyton (Achorion) schoenleini* or any of several closely related organisms. It is characterized clinically by saucer shaped yellowish scutula Infection may involve the *hair nails or glabrous skin, or all of these. The scalp is the commonest site.* A scutulum tends to enlarge peripherally and neighboring lesions coalesce to form thick, mortarlike masses which possess a peculiar characteristic odor like that of a mouse nest. The hair becomes dull, dry lusterless, and brittle In long-standing cases the follicles undergo atrophic obliteration, leading to cicatricial alopecia. The disease progresses tediously and it may endure over a period of many years. Favus is distinguished from tinea only by positive identification of the organism. Favids are the analogues of trichophytids.

Etiology —The disease may be transferred by handling infected animals, but transference from infected human beings is the usual route.

Treatment —The treatment of favus of the scalp is essentially that of tinea capitis. Roentgen epilation is highly desirable Morris (NEngJM 230 667 1944) was able to cure 2 Massachusetts cases in teen-age girls without epilation. Locally he alternated applications of 10% thymol in chloroform with 4% chrysarobin Carslaw (BJD 63 16 1951) reported that of 17 epilated cases, 12 were cured and 5 relapsed Parasiticides are those commonly used in tinea.

See Parker (JCutDis 3 44 1885) case, scalp of infant Way and Weidman (CalifWM 36 322, 1932) A quinckeanum case from California Siemens (Nederl TijdschrGeneesk 79 5140, 1935) treat 11 members of family simultaneously Barrett (ADS 33 126, 1936) 8 Kentucky cases Husk (DMtsch 70 125, 1937) 9 cases in one family several with f vids Aitken (EdinMJ 4 867 1938), 9 cases in Royal Infirmary in 20 years Montgomery et al (ADS 38 884 1938) nail only M and h rotchkin (ChinMJ 55 701 1939) 93 cases Muskatblit (MRec 151 187 1940) 6 New York t l rnty cases Machee et l (NYSJM 41 1722, 1941) x-ray epilation, salicylic acid and sulf followed by ammoniated mercury ointment; Swartz and Rockwood (ADS 41 415, 1943), in four generations; Kaplan and Hamblet cheek (Dermatologica 93 110 1946) 3 cases of f vic kerion on record; Russell (BJD 60 61, 1948) resemblance t folliculitis decalvans Robbins (ADS 58 180 1948) 3 New York cases Dobes (UCutRev 52 729 1948) 10 Georgia cases Upright and McCuiston (ADS 60



Fig. 464.—Favus, showing typical scutula. (Dr George Miller MacKee.)



Fig. 465.—Favus. (Dr Howard Fox.)



Fig. 466.—Favus of nails. (Dr M. H. Foster.)

1202, 1949) endemic in Texas, Barrett (SouthMJ 43: 685, 1950) Kentucky cases, dull yellow green fluorescence Fishman (ADS 68 38, 1953) epidemic in nurses, contracted presumably from clinic patient in a New York hospital.

Tinea Versicolor (Pityriasis Versicolor) is a superficial dermatomycosis due to *Malassezia furfur* Yellowish or brownish macules are found usually on the chest and shoulders, although involvement of various regions, including



Fig. 66 —Tinea versicolor



Fig. 668 —Tinea versicolor

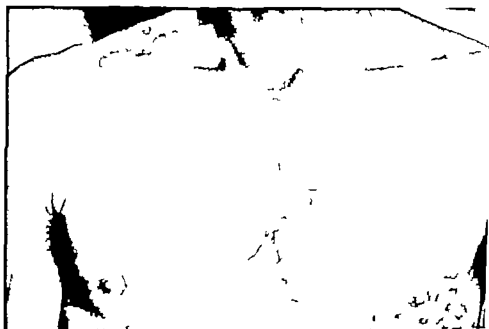


Fig. 669 —Tinea versicolor (Dr Ham) (F Itzer)

the scalp and even generalized cases have been seen by Costa and Junqueira (ADS 47 646 1943) In 47 cases of Bumgarner and Burke (ADS 59 192, 1949) 9 showed involvement of the scalp 2 of the face and 12 of the neck These authors believed that undiagnosed and untreated lesions of neck and scalp may serve as foci explaining persistency or relapse of the disease after treatment.

The patients are generally adult. The disease begins with one or more small, rounded, noninflammatory macules which enlarge slowly and may reach a diameter of 3 cm. or more their surfaces being covered with fine scales. Symptoms are almost wanting as a rule The lesions are usually followed by leukodermic patches into which pigment eventually returns (Adamson BJD 61 322, 1949) A peculiar musty odor is readily detected about persons who are extensively involved.

The lesions may clinically be practically invisible made manifest only by exposure of the skin to sunshine which induces pigmentation of the unaffected skin (Gougerot: BSocfrançD 43 1596 1936) Such lesions are miliary fixed and of minute dimensions. Despite their inconspicuousness they contain the parasites abundantly They may occur in patients with ordinary visible patches.



Fig. 470—Tinea versicolor unusual location. (Dr O G. Costa.)

Etiology and Pathology.—*Malassezia furfur* is easily detected in scrapings immersed in 10% KOH. Cellophane tape applied to a lesion pulls off readily identifiable fungus-laden material (Porto JID 21 229 1953) The parasite has been cultivated by Moore (AD&S 41 253 1940) Persons with moist warm skins, such as sufferers from tuberculosis, seem especially liable to infection There must exist some unknown susceptibility of the host for it is common to find the infection in one spouse and not in the other

Treatment.—The disorder is harmless and responds favorably though seldom permanently to medication. The skin may be swabbed with half saturated sodium thiosulfate solution and allowed to dry then swabbed with 5% vinegar this frees nascent sulfur and sulfurous acid (compare Scabies, treatment) Three per cent salicylic acid with 6% benzoic acid and 5% precipitated sulfur in petrolatum will serve well This should be applied over the entirety of the affected regions of the body twice a day for 2 days, then washed off The patient dons clean garments and sterilizes or dry-cleans contaminated ones. Such a course of fungicidal ointment therapy may be repeated after a month An ointment containing 5% crude coal tar is messy but effective.

Tropical Tinea Versicolor.—Yellow white and black forms have been described (Castellani: JCutD 20 393 1903) The neck and upper part of the chest are most often involved. Compare Lepothrix (p. 505)

ACHROMIA PARASITARIA.—Depigmentation may result from superficial fungus infections of a sort resembling tinea versicolor. There appear dirty whitish spots, slightly inflammatory at first but soon losing this aspect, becoming scaly and eventually becoming quite devoid of scales. After depigmentation has occurred, the lesions resemble those of vitiligo or syphilitic leukoderma (Pardo-Castello: ADS 25: 785 1932) See Vitiligo with raised borders; Pityriasis simplex.

PSEUDOACHROMIA PARASITICA is an interesting and by no means rare condition resulting from exposure to sunshine of a skin infected with tinea versicolor. This is followed by normal hyperpigmentation of the normal skin between the mycotic macules, while the fungi of the infected macules themselves are opaque to the tanning rays yet are destroyed by actinic energy, so that the lesions desquamate, fade and heal, leaving depigmentation in their places. The patient's appearance is then analogous to a photographic negative of his former appearance.



Fig. 671.—Achromia parasitaria. (Pardo-Castello ADS 25 785, 1932.)



Fig. 672.—Tinea versicolor after ultra violet irradiation, showing reddening of skin between opaque patches of dermatomycosis pseudoachromia parasitica.

See Lewis and Hopper (ADS 34 850, 1936) scales positive for fungi in pseudoachromia, lesions of which show typical fluorescence Marquardt (DWchn 104 177 1937) cultures of M furfur in Grütz' medium Jiner (ADS 27 870, 1933) scalp involvement, quotes Suzuki (JOrientM 8 97, 1928) on unusual locations Moore (ADS 38 349, 1938), pubic region Jiner and Barston (ADS 44 676, 1941) scalp Carpenter (ADS 47 251, 1943) face, in infant McCarthy (J 123 449 1943) tropical tinea

Erythrasma.—*Nocardia (Actinomyces) minutissimus* is a delicate fungus with spores and myceliums about 1 μ in diameter It has not probably been successfully cultivated It produces irregular but sharply circumscribed, reddish brown, slowly spreading finely scaling dry patches of slightly pruriginous, superficial dermatitis, located usually in the axillary genitocrural or pubic regions, rarely elsewhere The patches develop and spread slowly and give rise to slight symptoms. Interdigital cases with desquamation and maceration were identified by staining the scales by Rabeau and Guerra (BSocfranςD 43 464 1936) See McCarthy (J 123 449 1943) Charac

teristic bright red fluorescence is seen under Wood's light in most cases but not all and such examination is useful in diagnosis, especially when the location is atypical (Michaelides and Shatin ADS 65 614 1952)

The antiparasitic medicines used in treating tinea corporis are appropriate, and garments should be sterilized to avoid reinoculation. The 8% solution of chrysarobin in chloroform so effective in dry tinea and mycotic paronychia is good, but it must be used with circumspection, being capable of blistering the patient.

Etiology of Mycotic Infections.—These are common dermatoses. Moisture, warmth, and darkness are predisposing environmental circumstances. Infection may occur immediately or through contact with contaminated articles such as towels, slippers and bath mats. Mycotic infections of animals are readily transferred to human beings, sources being cats, dogs, horses, cattle, and even birds. Epidemics are commonplace, and schools, armies, and other communities where personal contact is close are subject to them There



Fig. 471.—Erythrasma. (Dr George Miller MacKee.)

are individual differences in susceptibility to infection, but lasting immunity apparently develops in no one and reinfections are common. Marital contact is not an important factor thought Sulzberger et al (ADS 45 670 1942) noting the paucity of reports of familial transmission.

The infection may lie dormant over long periods of time, only to flare suddenly when circumstances favor the growth of the organism. Autogenous reinfection was impugned as the principal mode of reactivation by Williams (ADS 18 730 1928) who demonstrated that nails often harbor inconspicuous but detectable infection. Shoes may be infected with epidermal scales which reinfect, and in such cases should, I believe be discarded rather than disinfected, for disinfectants like Formol are often irritating Inoculation with fungi occurs especially under conditions of close contact with infected persons, in sleeping quarters, locker rooms, swimming pools, showers, etc. The parasites find some individuals to their taste and others less attractive, and it is commonplace to observe a husband with chronic tinea pedis while his wife shows no trace of the disease and this is also notably true of tinea versicolor

TINEA IN INDUSTRY —The careful study of Peck et al. (ADS 50 170 1944) who surveyed the significance of tinea in 2,123 workers yielded no indication that infection with fungi and allergy thereto were related to the acquisition of dermatitis venenata. Tinea was not an important cause of loss of time in industry. There were three times as many cases in summer as in winter and about one third of all workers showed clinical evidence of the disease. See Downing (J 125 196 1944) Schwartz (OccupM 3 543 1947)

Dermatophytid.—In mycotic infections there may occur widespread, disseminated eruptions due to allergy to fungi (Low BJD 36 432 1924). Dermatophytid is the general name for such eruptions, which may differ widely in appearance. Epidermophytid, moniliid, and trichophytid are specific names applicable when the specific causative agent is known. The incubation period is about 10 days. The eruption may follow x ray or dermatomycin treatment. It may be violent or mild. During it the specific test is always positive and is generally accompanied by focal flare. It occurs when the primary site is actively vesicular or inflammatory. See Sulzberger (ADS 18 801 1928)

TYPES OF DERMATOPHYTIDS.—Lichen trichophyticus is the name applied to a dermatophytid occurring in tinea of the scalp, *in which the eruption is composed of scant* or numerous small red papules located on the back and shoulders, becoming scaly as they disappear (Williams ADS 4 353, 1921). Dermatophytic erythema multiforme and erythema nodosum have been seen. The commonest dermatophytid is pompholyx (q.v.) of the hands in vesicular tinea *of the feet* (Peck: ADS 22: 40 1930). If the focus is not con*trolled, the eruption may spread to involve the arms in scattered, discrete and confluent* patches of erythema, later becoming eczematous and scaly. The sides of the neck and the face may become involved. Erysipelas-like, recurrent dermatitis of the lower extremities was recognized as an "id" by Traub and Tolmach and by Sulzberger et al. (J 105: 187, 150 1937). Inflammation is less intense and more diffuse than in erysipelas. The lesions *recur in patches of constant size, shape, and location, as fixed drug eruptions do, noted* Walzman (ADS 53 10 1946). *His* patient manifested the usual immediate wheal reaction when trichophytin was injected within the area of the lesion. Hyposensitization was not successful when allergen was injected into normal skin, but was when injected within the lesion, following which the immediate reaction was reduced but not the 48-hour type *of reaction. Passive transfer of reactivity was demonstrable as is usual, in Walzman's* carefully studied patient in whom specific hyposensitization was obtained despite the persistence of positive skin reactivity and of Prausnitz Küstner reagins.

ETIOLOGY AND TREATMENT —*Dermatophytids are free from demonstrable* fungi. They depend on hyperergy to products of fungi (Sulzberger et al. ADS 34 207 1936). Dermatophytids tend to occur in showers and to disseminate symmetrically and the blood culture may be positive (Peck JIndianaMA 37 304 1944). Injections of trichophytin into the skin regularly reduce sensitivity and increase tolerance and hyposensitization so produced is sometimes accompanied by clinical improvement but there is seldom satisfaction in treating tinea and its allergy by means of trichophytin. One does better to attack the foci with appropriate means and in treating the "ids," to use bland nonspecific remedies such as 1:600 aluminum acetate for wet dressings or calamine lotion with phenol. Cortisone 75 mg daily accompanied by potassium chloride 30 gr daily for a few days may effectively counteract the patient's allergy during the period of time needed to bring the primary infection under control.

Dermatophytids, especially the pompholyx type are susceptible to secondary bacterial infection. Many a case of chronic dermatitis of the hands is of this complex nature to be cured by accomplishing elimination of focal infection, including mycotic infection of the feet and toenails, and using locally 2 per cent sulfur in Vioform Cream modest doses of x ray therapy and a program of avoiding contact irritants.

DERMATOPHYTID.—See Schamberg (J 61 1328, 1908), pinpoint whitish scaling of palms distinct from pompholyx; Bott (ArDuR 137 736 1921) lichenoid exanthem in case of kerion; Williams (ADS 4 357 1921) dermatophytids, like those described by Rasch (BJD 32 317 1920) and Bloch (Amsterd, Feb 1921); McGlasson (ADS 14 670, 1926) recurrent erysipelas of legs and bacterial infection of pedal tinea; Whit (ADS 20 316, 1929) perhaps transplantation rather than hematogenous dissemination in "ids"; Williams (ADS 21 437 1930 23 313, 1931) rashes complicating tinea of groin and beard; Idem (ADS 37 972, 1913) dermatophytids; Wise and Wolf (ADS 34 1 1936) dyshidrosiform rashes on hand and feet are not necessarily due to fungi or allergy to fungi; Waldbott and Ascher (ADS 38 314,



Fig. 474.—Dermatophytid causing pompholyx.



Fig. 475.—"Keratolysis," a common type of dermatophytid. (Dr. Grover Wende.)

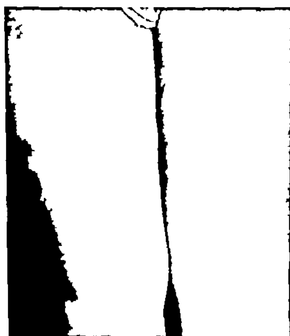


Fig. 476.—Urticarial and erythema annulare-like dermatophytid on the thighs of woman with acut vesicular tinea of feet.

1937) urticarial Reiss (JClinM 2, #1, 1938) relation of tinea of feet to inflammation of leg Yang (ChinMJ 57: 161 1940) recurrent erysipelas of legs Naide (AmJMedSci 20 : 82, 1941) fungus allergy and thromboangiitis obliterans Lasar (ADS 68 574 1953) erysipelas-like fixed eruption on leg.

DERMATOMYCOSES AND IMMUNOLOGY.—Vaccinal preparations of fungi have been studied with regard to their academic and practical significance. Reactions to trichophytin include the immediate urticarial reaction, the late tuberculoid inflammatory reaction to intradermal tests, and the eczematous reaction to patch tests. Efforts to obtain practical therapeutic results by the use of vaccinal agents may summarily be adjudged fruitless. Precipitins, agglutinins, and complement fixation antibodies circulate in human beings who are hypersensitive to dermatomycoses (Blumenthal: HandbHaG 11: 359, 1928). Thus vaccinal fungus materials can be used in diagnosis, much as tuberculin and luetin are used. Again the practical importance is slight because allergy from past infections, presently unimportant, may persist so that a positive test has no trustworthy significance as to the nature of the dermatosis at hand (Lewis et al.: ADS 38 713, 1938). The use of fungus vaccines in therapy, for immunizations, is recommended by some authorities, especially in attacking certain cases of pruritus ani, but I have found the measure disappointing. Of 65 patients treated with vaccines by Tolmach and Traub (ADS 33: 925, 1936) 9% were favorably influenced.

IMMUNOLOGY AND IMMUNOLOGIC THERAPY.— Brunsgaard (ActaD-V 3: 21, 1922) generalized nodular eruption following trichophytin injection in case of kerion; Fried and Segal (ADS 19 93 1929) T. gypseum injected intravenously into rabbits resulted in lesions only in scarified areas of skin, where local inflammation abetted pathogenicity of parasite. Peck and Jadassohn (ADuS 161 16, 1930) trichophytin allergy demonstrated in superficial tinea. Sulzberger and Kerr (JAllergy 2: 11, 1930), immediate reactivity to trichophytin passively transferrable. Ramirez (MJ & Rec 132 332, 1930), asthma from intradermal trichophytin injection. Sulzberger and Lewis (ADS 22 410, 1930), eczematous reaction to trichophytin. Peck (ADS 22 40, 1930), immunology. Wieder (WiscMJ 32 225, 1933), immunology. Sulzberger and Wise (J 99: 1759 1932) desensitization with fungus vaccine; Kerr et al. (JAllergy 5 238, 1934) immunologic treatment of tinea. Templeton (JAllergy 5 521, 1934), trichophytin therapy. Schols (DWchn 99 1342, 1934) reinfection with Epidermophyton ran shorter course than initial infection. Földvári (DZtschr 70: 260 1935) complement fixation antibodies in deep cases, titer not necessarily affected by vaccine or therapeutic response thereto. Robinson and Grauer (ADS 32: 787, 1935) autogenous trichophytin therapy. Traub and Tolmach (ADS 32 413 1935), trichophytin hyposensitization not clinically valuable. Ehler and Kanarijian (NYSJM 36 Dec. 1, 1936), no great therapeutic value. Jadassohn et al. (JImmunol 3 93, 1937) antigens in trichophytin, Schultz-Dale experiments, no pure, single antigen found. Marcussen (ADS 36, 494, 1937) antibodies same in immediate and delayed reactions. Traub and Tolmach (NYSJM 38 365, 1938) vaccines valueless. Council Rpt on trichophytin and Oidiomycin (J 107 665, 1936 113, 1735, 1939). Lewis et al. (ADS 38 618, 1937) long delayed reactions representing induction of sensitivity by performance of test. Henrici (Third Internat. Congr Microbiol. 1939 p. 567) protein and polysaccharide fractions of T. mentagrophytes produce different effects in experimental animals, and polysaccharide appears to be antigen responsible for human blood-borne id. DeLamater (Third Internat. Congr Microbiol. 1939 p. 575) immunity in experimental tinea reaches climax in 5 months and disappears in 11 months, and tissues of healed animal are relatively immune to reinoculation, more so within actual site of previous, healed disease. Peck et al. (ADS 42 428, 1940), slight fungistatic property of blood serum of infected person. DeLamater (JID 4, 143 1941) allergy to T. gypseum in guinea pig rises to peak after lesions have been healed 2 or 3 weeks, then diminishes, while immunity develops and wanes similarly. Peck and Glick (ADS 43 879 1941), preparation of trichophytin. Miller et al. (ADS 44 904, 1941) preparation. Peck et al. (ADS 44 816, 1941) preparation. Fancher et al. (JImmunol 48 193, 1943) histology of trichophytin and Oidiomycin reactions not tuberculoid. Kattenstein (JID 8 240, 1947) specificity of skin tests with histoplasmin, coccidioidin, sporotrichin and blastomycin, no false positives in persons lacking deep mycotic infection. Jillson and Huppert (JID 12 179 1949), urticarial reactivity to trichophytin in T. rubrum infection and in patients with history of atopy or recurrent lymphangitis not abolished by hyposensitization injections, though tuberculoid reactivity was. Jadassohn and Suter (ActaAllerg 4 150, 1951), tuberculoid reactivity lacks demonstrable antibodies. Gotz and Three (DWchn 124 1102, 1951) trichophytin test of limited value.

Prognosis.—The outlook in mycotic infection varies with the location, extent and duration of disease, the specific cause, the reactivity of the particular patient and the effectiveness of treatment. Tinea corporis usually responds readily and favorably although *T. purpureum* infections are exceptions to this rule. In extensive cases of tinea of the scalp the infection is extremely rebellious in some cases, especially in *T. tonsurans* infections, and easier to cure in others, depending on the infecting organism. In cases in which kerion occurs, baldness due to scarring may result. Great care must be exercised in examining a case before discharging it as cured. *Good treatment, which implies attention to detail and to the following of correct broad principles is materially advantageous.* In World War II experience a wet tropical climate rendered cure without evacuation sometimes impossible. All infected areas must be treated simultaneously so that dissemination cannot occur. *Fungi, like bacteria, propagate fast* under suitable conditions. Animal and human sources of reinfection along with inanimate sources such as clothing and shoes must be recognized and dealt with. *Dermatitis venenata* due to medication must be recognized and avoided. Secondary coccic infection is commonplace and *focal infections must be eradicated* in many a patient before cure of what appears to be chronic *tinea of hands or feet can be achieved.*

Treatment of Tinea.—Correct diagnosis is essential. The distinction of tinea from dermatitis venenata and from coccic disease is important. Tineal dermatitis is due to moldlike fungi which primarily parasitize the dead horny cells of the epidermis and secondarily provoke inflammation allergy anti body production and eczematous dermatitis. In regions where the fungi are treatment aims at eliminating them by removing some mechanically and in hibiting the others with chemicals that do not injure the skin. In the lesions due to allergy the aims are (1) attacking foci whence dissemination originates and where fungi are present and (2) soothing the inflamed skin where pathogenic fungi are not present, so as to give the patient symptomatic relief.

Many chemical substances are serviceable and none of them is specific (Kingery et al. JLabClinM 20 950 1935) The physician undertakes not to exterminate parasites, but rather to tip the equilibrium between host and parasite in favor of the host while one trusts to the natural responses to attend to the healing.

The antitheses of moisture warmth and darkness are prescribed, while suitable débridement may deprive the parasite of its cultural medium and mechanically remove large numbers of them

In acute vesicular lesions, astringent soaks and antiseptic powders are serviceable. Vesicles should be opened widely so that antiseptics can get into them Inflamed skin treated with soaks and without grease readily becomes cracked and fissured if it is flexed but it regains its normal flexibility when the inflammation disappears. The use of unguents, while comforting is here likely to disappointment. Medicines must be stopped before they do harm. The plan of treatment must be individualized.

Obesity predisposes to mycotic infections. In diabetes the sweat is laden with sugar which serves as pabulum especially for Candida. Tight clothes keep the crural regions continually moist and ill ventilated so that tinea of the crotch may be impossible to cure until these conditions have been altered Shoes which are tight across the toes, holding them in continuous juxtaposition, make it next to impossible to cure interdigital tinea.

Internal remedies of value are few indeed. Arsphenamines are decidedly dangerous as well as useless, for the sensitivity of the skin is precarious during mycotic infection. Vaccinal therapy has been disappointing see Dermatomycins. Prantal given in suitable dosage to inhibit volar hyper hidrosis, may contribute materially in handling some cases, 50 mg 4 times a day sufficing for most adults.

Roentgen therapy in treating tinea must be used with greater wisdom than in most other conditions for which it is useful. X ray energy does not kill the fungus. It may reduce hyperhidrosis, and it abets dissolution of in flammatory reaction and helps to cause vesicles to resorb (Brundage South MJ 31 1097 1938) It inhibits the ability of the skin to respond to the presence of the fungus, and its use is generally followed by several days of remission. When roentgen therapy is used time after time as the disease repeatedly reappears the result is atrophy or burn.

USEFUL CHEMICAL AGENTS

Soap and water along with a scrubbing brush sometimes perhaps rei f rced with sandpaper for attacking thick collections of scales in chronic squamous tinea f the feet.

Soaks and Compresses such i

Potassium Permanganate (3 grains to the gallon of w ter)

℞ Pot sium permanganat 0
W ter 100.0
Sig.: 1 teaspoonful to 1 quart water for soaks, douches or compresses.

BICHLORIDE OF MERCURY 1:10,000:

℞ Bichloride of mercury 1.0
Water 20.0
Sig: POISON 1 teaspoonful to 1 quart water for soaks or moist poultices.

ALUMINUM ACETATE (half a teaspoonful to the quart of water)

℞ Aluminum acetate powder 2.0
Put equal portions into 10 capsules.
Sig 1 capsule to 1 pint of water for moist packs.

CHRYSAROBIN 1% dissolved in chloroform, especially serviceable for tinea of nails after débridement, and on dry superficial tinea of crural or axillary folds, between the toes, or (with caution—it is hot!) about the anus.

SILVER NITRATE, 5% in water for occasional topical application, serving as a protein precipitant capable of rendering the epidermis uninhabitable

IODINE, the tincture, for painting infected nails.

SALICYLIC ACID 3% in 1 1 000 tincture of Merthiolate is useful for chronic vesicular tinea. The 10% alcoholic solution of salicylic acid is popular It causes scaling not to be confused with tineal disease

GENTIAN VIOLET *% aqueous solution, is fungicidal for gram positive organisms, not toxic, and astringent Methylene blue, 1% aqueous, yields a more flexible crust than gentian violet. Brilliant green and acriflavine have been advocated (Loos AfDu# 170: 602 1934 McCrea: Mycologia *6 449 1934) Gentian violet may irritate mucosae severely

DUSTING POWDERS such as:

(1) ℞ Camphor 1.0
Salicylic acid 1 0
Zinc oxide
Cornstarch
Zinc stearate .... of each sufficient to make 100.0
Sig: Dust between toes and into shoes to keep feet dry

( ) ℞ Salicylic acid
Menthol .... aa 1 0
Thymol iodide
Boric acid
Zinc oxide
Talc .... aa 10 0
Sig Antiseptic powder (favorite of Duemling: ADS 5.: 75 1945)

(3) Desenex Powder a proprietary zinc undecylenate preparation recommended in interdigital and intergluteal or crotch infections. (See Fatty acid therapy)

WHITFIELD'S OINTMENT (see BJD 56 .3 1944 59 173 184)

℞ Benzoic acid 5 0
Salicylic acid 3.0
Soft paraffin 5.0
Coconut oil .... t 100.0

Modification of Whitfield's ointment include the National Formulary one:

℞ Benzoic acid .... 1..0
Salicylic acid 0.0
Wool fat 5.0
White petrolatum .... to 100 0
Sig Whitfield ointment NF full strength.

Practical modifications of Whitfield's ointment NF include the addition of 1% phenol perhaps dilution with petrolatum or Lassar's paste to half strength or the incorporation of from 3 to 10% precipitated sulfur

SCHALEK'S PASTE an excellent antiparasitic agent

℞ Phenol 0.3
Salicylic acid .... 1..
Precipitated sulfur 1 6
Zinc oxide
Cornstarch .... of each 4 to 8
White petrolatum .... to 30.0
Sig: Rub in twice daily wash off with soap once daily

DENNIE'S ORANGE OINTMENT a potent mercurial analogue of Whitfield's:

℞	Red sulfide of mercury	0.1
	Salicylic acid	3.0
	Benzoic acid	6.0
	Sulfur precipitated	2.0
	Lanolin	20.0
	Petrolatum	to 60.0

Sig Dennie's orange ointment fo fungus infection.

CASTELLANI'S FUCHSIN PAINT (BMJ 1 235 1943), a valuable parasiticidal lotion, the potent ingredient of which is resorcinol, and basic fuchsin inhibits monilia:

℞	Basic fuchsin, sat. alcoholic sol.	10.0
	5% aq. sol. phenol	100 0
	Mix, filter then add	
	Boric acid	1.0
	Acetone	5.0
	Resorcinol	10.0
	Filter	

Sig: Apply by swabbing several times a day

There are few cases of tinea which will not respond to one or a combination of the preceding correctly used. In the following list brief comments are offered regarding the virtues (or lack of them) of numerous therapeutic agents, and the tabulation with its references may be of service

Ammoniated mercury ointment (1 to 10%): parasiticidal, often irritating

Anthral (Dihydroxyanthranol) effectiveness m ch like that of hrysarobin (q v); useful, with caution, in 1% ointment or chloroform solution.

Antibiotics discussed under Treatment antibiotic, antifungal.

Antihistamine compounds: some fungistatic powe but their generally considerable tendency to irritate or sensitize has kept them from being acceptable (Carson and Campbell: Sci 111 689 1950 diphe ylpyraline; Sokoloff ADS 64: 764 1951 diphe yl pyraline; Carter and Sutton: JKansMS 52: 119 1951 Chlor trimeton; Seneca: Sci 115 48 195_) Fahlberg (JID *0: 171 1953) di Paralene best.

Asterol dihydrochloride: alleged to make x ray epilation unnecessary in treatment of tinea capitis (Stritzler et al. ADS 63: 606, 1951; Ravits: J 148: 1005, 195_) Parent neous absorption ha ca sed convulsions in infants (Wallach: ADS 67: 517, 1953; see Dermatitis medicamentosa) must be used correctly (Pirk a d Sevringhaus: ADS 67: 519 1953)

Benzoic acid (5 to 15%) a tiseptic antimold agent, apparently harmless as food preservative in 1:1,000 dilution, valuable with sali ylic acid n Whitfield's ointment and t modification (q v)

Betanaphthol (3 to 10%) parasiticidal.

Campho ph nol fungicidal(?) dangerous (Gle and Hailey: ADS 47: 259 1943, nfavorable Phill ps BJD 56 19 1944 favorab le)

Chlorine (hypochlorite, Cl rox, etc.) hazardous an l u reliable

Carvacrol a creosote-lik substance obtai able from campho l combin tion with chlorine and mercury (monochlormercuricarvacrol): fungistatic (Geo gi: ADS 48 497 1943)

Citric cid and i egar have practical utility: a good home remedy is to rub in fected ski with cut surface of a lemon (Alderson ADS 39 706 1939)

Chrysarobin 1 to 10%—da gerous about the eyes—potent, exfoliative rubefacient, reducing gent. Dihydro ya thranol (Anthralin) may be substit ted (Molitch: J 106: 1563, 1036) Useful i chloroform sol tion r l tment ehicle.

Cl icin (Herrick: PSExpBiol 59: 41, 1945): 0.5% topical, lethal to pathogens. See Antibiotics, a tifungal

Coppe sulf t : 1:5,000 aqueous, a good antiseptic soak. Copper undecylenate i Carbowax for se lp cases i good (Combes et al.: JID 10: 447 1948)

Copper sulf te iontophoresis (Greenwood and Rockwool ADS 44 800 1941; Haggard et l: J 11_ 1229 1939) 0.2% aqueous solution of copper sulf t i pans to immerse extremities to be tre ted, othe tremities t be immersed i simila pans containing isotoni saline sol tion Th pos ti lectrode is connected t the coppe solution, the negativ t the sali A curre t of bout 5 milli mperes i used to treat on ha d or foot 5 t 10 mn. if both hand both feet are treated sim ltaneou ly Iontophoresis is so carried out for periods of bout 30 m tes, 3 times week. Best result obtained i active, vesicular cases. Fi l trate b iontophoresis, see Harpuder (NYSJM 39: 176 1939)

Crud coal t : t 50% in lan lin and petrolatum messy but effectively antiparasitic, rarely irritating

Dithiocarbamate derivatives: fungicides not inactived by blood (Kligman and Rosensweig: JID 10: 59, 1948)

Essential oils: most effective include those of neroly geranium, linalool, citronella; particularly derivatives of phenolic type and the doubly unsaturated acyclic terpenes (Vilanova and Casanovas: JID 20: 447 1953)

Ethyl chloride spray: defatting desquamative rubefacient (Lewis and Morginson: ADS 50: 243, 1944 Bograd ADS 48: 511 1943)

Ethyl iodide inhalation (Swartz: ADS 40: 962 1939)

Ethylparaoxybenzoate and allied fungicidal substances: investigated by Bonnevie (ActaD-V 17 576 1936) who commended them and also thymol, and benzoic, salicylic and cinnamic acids.

Fatty Acid Therapy—See Sulzberger and Kanof (ADS 55: 391 1947); Muskatblit (ADS 56: 256, 1947); Keeney et al. (BullJHH 73 479 1943, 75: 377, 393, 410 417 1944; 77 421, 1945) sodium caprylate ointment Peck and Russ (ADS 56: 601, 1947) propionate-caprylate mixtures, review and bibliography Bereston (JID 8: 227 1947; 9: 243, 1947) propylene glycol dipropionate useful for tinea of the feet but not superior to other agents in common use, and ineffectual in M audouini infections of the scalp; Nettleship (ADS 61: 609 1950) propionate-caprylate ointment and powder good. Undecylenic acid derivatives (Shapiro and Rothman: ADS 5_: 166 1945) Desenex ointment preferable to Sopronol zinc undecylenate enhances fungicidal activity (Sullivan and Fishbein JID 10: 293 1948) See T purpureum infection (p. 509)

Formaldehyde: 3% for soaks; hazardous, often irritating; has been advocated to sterilize shoes. See Salsbury (CanadMAJ 36: 515 1937)

Iodine the tincture—incompatible with sulfur and mercury—antiseptic (Sharlit: ADS 40: 663, 1939)

Iodocholeate, a crystalline bile salt of iodine, 10% in a water containing vehicle (Lever: ADS 40: 19 1939)

Mercurochrome followed by ultraviolet light (Gomez Vega ADS 34: 961, 1936)

Mycostatin: antifungal antibiotic valuable in *Candida albicans* infections (see p. 530)

Naftalan a tarry antiseptic approved by Ormsby (NEngJM 224: 673, 1941)

Parabens, methyl and propyl: low in toxicity not interfering with antibiotic action of Aureomycin or penicillin (Siegel: AntibiotChemoth 3 478, 1953)

Perchlormethyl Mercaptan reacting with alkali metal salt of imides and amides: mainly colorless, odorless crystalline compounds, some apparently effective (Kittleson: Sci 115 84 1952)

Phenol: 1% antipruritic, mildly antiseptic.

Phenyl Mercuric Compounds usually irritating, of little clinical value despite in vitro effectiveness (Goldman et al.: ADS 47: 569 1943)

Resorcinol 3 to 10% similar to salicylic acid.

Salicylanilide with TCAP in Carbowax good in tinea capitis (Schwartz et al.: IndustM 18: 257 1949; Hopkins et al. ADS 67: 479 1953)

Salicylic acid 2 to 10% provocative of desquamation not strongly antiseptic it self Valuable in combinations with benzoic acid and sulfur Salicylic acid in alcohol is often used to induce exfoliation The formula favored by Albert and Zeigler (SouthMJ 3 348 1944) was

℞ Salicylic acid — — 10.0
Acetone
Ethyl alcohol (85%)
Glycerol — — of each to make 100.0
Sig Swab on fungus infection daily for a few days.

Silver Nitrate: 5% aqueous for occasional topical application; soaks 1:5 000, astringent and parasiticidal. Saturated alcoholic solution for nails. Ammoniacal silver nitrate allegedly penetrant, disappointing

Spergon (tetrachloroparabenzoquinone): 5 to 50% in ointment bases tested by McGavack et al. (ADS 59 94, 1949) with cures of tinea capitis. Its in vitro effectiveness is high (Gordon: ADS 66 573, 195_) It obscures fluorescence of infected hairs and produces false cures, according to Moore (ADS 66 621 1952)

Sodium Borate: 2% soaks or as powder for feet See Ingels (CalifWM 54: 129 1941); Dóza (AfDuS 176: 281 1937)

Sodium Thiosulfate isotonic to saturated solutions, weakly antiparasitic sometimes irritating, usefulness overestimated.

Stilbamidine and related compound see Blastomycosis, treatment. Propamidine in treatment of tinea was investigated by Fison (JInfectDis 76: 193, 1945); salicyl and related benzestrol and diethylstilbestrol show antifungus activity (Heinemann JID 9: 277 1947)

Streptothricin 10 unit per gram in greaseless ointment base for anterior genital tinea (Greer ... J 129 101_, 1945)

Sulfonamide sulfanilamide best inhibit T gypseum not C albicans to be given internally not to be applied topically for actively inflammatory disease (Lewis and Hopper: ADS 44: 1101 1941)

Sulfur: 3 to 15%, excellent fungicidal agent activity enhanced by combination with salicylic acid. Vioform ointment is a good vehicle adding antibacterial effect.

TCAP (trimethylcetyl ammonium pentachlorphenate): with undecylenic acid is active and effective, according to Foley and Lee (JAmPharmAssn 36: 1?? 1947; JID 8: 1 1947 10: 49 1948)

Tetrachlorphenol sodium: ?% with 3% salicylic acid added to the ointment, effective (Wieder: ADS 31: 644 1935)

Tetraiodomethenamine in collodion releases iodine slowly (Sharlit: ADS 40: 603, 1939)

Thymol: 0.5% or weaker fungicidal, apt to irritate

Undecylenic acid derivatives: see Fatty acid therapy

Vioform: 3% cream or ointment adding 3% precipitated sulfur; valuable in monilial disease and secondarily infected tinea.

Zephiran: antiseptic recommended by Hopkins et al. (BullUSAMD June 1944, p. 43)

Zinc chloride: 1/100 molar (1.7 Gm. per liter) permanently inhibits respiration of fungi (Nickerson: Sci 103: 484 1946)

Evaluation of Fungicides.—The methods of testing have received extensive consideration. To effect clinical benefit the vehicles are likewise of concern. While fungicidal agents can diffuse from collodion films, fluid vehicles seemed preferable to Sharlit (ADS 31: 17 1935) Ointments were of especial interest to Burlingame and Reddish (JLabClinM 24: 65, 1939)

See Kingery et al. (JLCM 20, 950 1935) phenol derivatives Weidman et al. (J 128 ???, 1945); Horsfall (Fungicides and Their Action, Chronica Botanica, Waltham, Mass 1945); Kligman and Rosensweig (JID 10 15, 1948) Peck (abs YBD 1949 p. 443); Bumby and Stewart (BJD 61 318, 1949) China et al. (JID 20: 177 1953) halogenation of test substances fungistatic activity increased by chlorination and bromination, not by iodination or fluorination, Rebell and Lamb (JID 21: 331, 1953) in vitro study of several blocked steroids, Lyons and Livingood (ADS 68 ???, 1953), improved method of evaluation H et al. (ADS 70: 1, 1954), tissue culture technic intended to duplicate in vivo conditions Curtis et al. (ADS 70 7??, 1954) antifungal activity of many compounds related to stilbenes; Barlow and Chattaway (JID 24: ??, 1955) effect of fungicides on keratin cross linkages and so on susceptibility to fungus attack.

TREATMENT OF REGIONAL TINEA

TINEA CORPORIS.—The disease as a rule responds to any of the parasiticides, such as Whitfield's ointment or Schalek's paste. This may be rubbed in repeatedly until the skin becomes slightly sore and scaly then treatment should be stopped for several days while one waits to see whether more is required. A single application of 3% chrysarobin in chloroform or of 0.5% Anthralin ointment may vigorously irritate and peel off the disease.

TINEA OF THE FEET AND HANDS.—Not a high proportion of what one sees called tinea of feet or hands is fungus infection in whole or even in part. Whitfield's ointment is unsuitable for coccic infection, dermatitis dependent on focal infection or contact, atopic or lichenoid dermatitis, which are of frequent incidence. However when tinea is the correct diagnosis, circumstances favoring the organisms may be altered by washing the feet with soap each night, rinsing them well and wiping away scaly accumulations. The toes should be dried carefully after bathing. A dusting powder is then useful. The shoes should be loose particularly at the toe. Vesicles should be opened and the feet soaked in some antiseptic foot bath such as 1:5 000 potassium permanganate or 1:10 000 bichloride of mercury. The soaks may last 10 minutes 2 to 6 or 8 times a day using cool water. In severe cases the patient should be off his feet which between soakings should be elevated dry and exposed to the air.

In chronic infections, with interdigital maceration and scaling about the toes and on the soles, daily washing and dusting are advisable. Silver nitrate is useful the 5% aqueous solution being occasionally swabbed over the involved areas. Ointments which provoke scaling such as Schalek's paste or half-strength Whitfield's ointment may be rubbed in once a day after the feet have been washed with soap and water. Scaling provoked by medicament must not be mistaken for scaling provoked by infection. The ointment should be used for several days, then omitted for several days.

Nails must be examined and treated appropriately. See Onychomycosis.

X ray therapy directed at the entire sole for control of hyperhidrosis may be advisable but it will not cure psychosomatic excessive perspiration. Prantal 50 mg q.i.d. may reduce sweating markedly while it is given and so aid in tinea associated with hyperhidrosis.

Medication of shoes or socks results in more harm than benefit, I believe. Reinfection comes from infected nails or other sources and permanent cure is not to be promised or indeed even sought. Physicians themselves often carry tinea of the feet for years, neglecting it when it is not bothersome.

In so-called fungus infections of the hands, *Ayres and Anderson* (CalWM 56 63 1942) demonstrated fungus organisms in only 12% Monilia comprised about one-fourth of these. Kerion is seen in persons who handle animals.

Prevention of pedal dermatomycosis may be accomplished by keeping the feet clean and dry wiping between the toes after bathing and using a nonirritant fungicide such as Desenex powder (Schwartz OccupM 3 543 1947) In the tropics, Jolly (BMJ 1 726 1948) prevented spread of the disease by *supplying each soldier with 2 clean towels, wooden clogs and a foot powder* treating bodily lesions as they were discovered with 1% chrysarobin in Lassar s paste and interdigital lesions with 1% brilliant green plus 3% salicylic acid in alcohol.

Tinea of Hands and Feet.—Peck (ADS 33 40 1936) epidermophytosis Osborne et al (NYSJM 34 1270, 1934), sodium hypochlorite as prophylactic Gray (BMJ 2 541 1934) feet Wilson (ADS 30 641 1934) cleanliness Wise and Wolf (J 107 1126, 1936), favorite prescriptions Elson (UCutRev 40 737 1936) sodium perborate in acute cases, 12% balsam of Peru in subacute Hein and Rosenblum (MRec 145 363, 1937), phenyl mercuric nitrate, frequently irritating but effective Jamieson and McCrea (ADS 35 201, 1937) pathogens cultivated from shoes Moloney (IANDIII 35 440, 1937) 20% $CuSO_4$ in glycerol; Trebs (J 111 686, 1938) 5% salicylic acid, 2% menthol, 5% camphor in starch and boric acid powder Goldman (OhioSMJ 34 408, 1938) favorite prescriptions, bibliography Metedy (MilSurg 83 260, 1938) sodium thiosulfate Epstein, Lewis, Loveman, Pillsbury, Schoch, Shelmire, Smith, Swartz, Wieder (JID 2 423, 1940) methods and prescriptions Peck and Schwartz (PHRpts 59 337 1944) favorite prescriptions Wallace and Moorman (ADS 47 814, 1943) in high school children Crittenden and Joiner (JLCM 29 898, 1944) rinse hose in copper acetate solution Pardo-Castello (ADS 49 222 1944) 100% coal tar for interdigital maceration Caro (J 124 761 1944) clinical features of *T gypseum T purpureum* and *E floccosum* infections, Sulzberger and Kanof (USNMB 46 821, 1946), undecylinic acid prophylaxis Rees (CalifM 69 28 1948) 3% salicylic acid 4% benzoic acid in 40% alcohol

Onychomycosis is an extremely persistent disease. The infection may be only superficial, but it is usually deeply situated where fungicides cannot reach the organisms. Thus the main dependence in treatment is upon mechanical removal of infected nail substance Nail nippers and an electric grinding tool are indispensable and as much infected tissue as possible should be removed once or twice a month. *After débridement one may apply* silver nitrate in saturated alcoholic solution or tincture of iodine or 3% chrysarobin in chloroform *During intervals between débridement procedures*, the nail *may be treated with Whitfield s ointment or a modification of it to include* sulfur but a patient seldom performs débridement for himself correctly

A nail grows distally about 1 mm per week while the fungus invades proximad If it can be brought about that the rate of invasion of the pathogen is less than the rate of growth of the nail success is eventually obtained, but it is tedious and hard won If cure is achieved in a year the treatment may be considered good Some cases especially those caused by *T purpureum* are practically incurable by methods presently in use Even avulsion is seldom *advisable* (White J 103 1370 1934)

Removal of Nail.—While Wigley (BMJ 2 390 1943) and Taylor (J 1 8 750 1945) have described the technic of surgical ablation of a nail, Montgomery (J 120 647 1945) advised conservatism using painstaking débridement and strong fungicides. Ablation of all nail substance is difficult, but avulsion is simple and is sometimes appropriate *T rubrum* onychomycosis is hardly curable otherwise so is chronic onychial moniliasis.

The digit is anesthetized by procaine injection subcutaneously into both sides of the proximal phalanx A rubber band is wrapped about the middle phalanx after anesthesia is achieved, in order to secure hemostasis. A No. 15 Bard Parker blade is pushed under the nail and *from* side to side working proximad under the proximal nail fold. The loosened nail is grasped with a strong hemostat and gently pulled forth while it is being lifted up Epidermis adherent to the root of the nail is thereby stretched, and it should be separated from the edge of the proximal nail fold to which it attaches. The nail bed is carefully scraped free of all infected epidermal material. The rubber band

is then removed from the digit, and a dressing of bland grease is applied. Little pain ensues, and soft nail substance covers the nail bed within two weeks. The nail root is unharmed, and normal regrowth may be hoped for. Avulsion may be repeated six months later if the previous effort failed to accomplish a cure.

Onychomycosis due to *T. purpureum* where little or no vesiculation of plantar skin appears, was discussed by Montgomery and Caspar (J 128 77 1946). The free edge of the nail is first affected, then yellow streaks extend longitudinally under the plate enlarge and render the nail yellow brittle and dystrophic so that it may detach. They used repeated débridement with an electric drill and applied 40% salicylic acid plasters to be changed weekly later tincture of iodine or 1 to 2% chrysarobin ointment. This disease is one that is really discouraging. A competent dermatological friend of mine has given up trying to cure himself.

NAILS.—Nickerson and Whit (AD&S 57: 926, 1948) ammoniacal silver nitrate. Fischer (Dermatologica 98: 237 1949) dissolve nail plate with calcium thioglycollate paste then reach parasites with fungicide. Franks and Sternberg (AD&S 62: 787, 1950) ammoniacal silver nitrate. Rothman (AD&S 67: 230 1954) hypothetic relation of glucose metabolism and susceptibility lithium bromide-glucose applications. Kesten et al. (AD 71 52, 1955) modified Rothman method, using lithium bromide and Asterol, 2 of 12 cases claimed cured.

TINEA OF THE CROTCH AND AXILLA commonly depends on the presence of infection elsewhere, particularly of the feet, which must be examined and treated appropriately. Chrysarobin in chloroform is my favorite remedy but its use must, in hot cases, be preceded by a day or two of boric acid or $KMnO_4$ compresses. Desenex powder may work well. The application of 5% silver nitrate and the use of 1:10 000 bichloride of mercury as cool wet poultices, applied for 10 or 15 minutes 2 to 6 times a day generally serve to control the infection. The underwear and trousers must be loose so that the parts are well ventilated. Schalek's paste may be rubbed in, left on overnight and washed off with soap and water the next morning. In women mycotic infection of the crotch is often due to mycotic vulvovaginitis, and 1:5 000 potassium permanganate douches twice a day should supplement external medication. X ray therapy in 100-r doses often helps greatly.

TINEA OF THE BEARD.—Localized inflammatory mycotic infection, kerion, is treated by the removal of loose hairs, the application of wet packs of 1:10 000 bichloride of mercury and small doses of roentgen therapy. Sulfadiazine by mouth may be helpful. When the infection is disseminated and chronic rather than deeply inflammatory and localized, the problem is more difficult. Then roentgen epilation and 2% sulfur in Vioform Cream may prove successful. Disseminated chronic tinea of the beard is a very rare disease not to be confused with sycosis barbae.

TINEA OF THE SCALP is often epidemic among children. Prophylactic measures are essential, and this involves isolation and control of tonsorial sanitation. The hair should be closely clipped, and a snugly fitting cheap cap should be worn continually. The scalp should be washed with nonmedicated soap and water once a day or once in 2 days, depending on its soreness. Infections with *Microsporum audouini* are highly resistant as a rule but not always. Livingood and Pillsbury (JID 4 43 1941) cured 70% without x rays. These are only sometimes inflammatory and are often hard to cure unless x ray epilation is done. *M. canis* infection may be treated successfully by showing the mother how to remove all infected hairs with a good forceps, with instructions to shampoo the head daily and to follow drying after the shampoo with a thorough rubbing in of 4% salicylic acid and 6% sulfur in petrolatum. Alternate use of 10% ammoniated mercury and 5% Mercurochrome served well for Cleveland (CanadMAJ 36 38, 1937). MacKee et al. (JID 7 43 1946) reported a topical method involving trimethyl cetyl ammonium pentachlorphenate, citric and propionic acids, and a detergent vehicle. Salicylanilide 5% or copper undecylenate saturated solution in Carbowax was effective in the Hagerstown, Md. epidemic of 1944-1945 when properly used (Schwartz et al.: J 132 58, 1946).

Roentgen Epilation may be judged safe if performed expertly with a reliably calibrated x ray machine. A tinea marker is simple and convenient. It consists of a flexible plastic band which fits about the head equatorially and has two bands attached to it which cross the scalp in great circles at right angles to the circumferential band and to each other. The circumferential band is located 5 inches, plus or minus ¼ inch or so, from the vertex intersection of the perpendicularly crossed bands which are placed so that one of them lies in the medial plane. Five points are thus marked by the vertex point and the four points 90 degrees apart on the circumferential band. The point over the middle of the forehead is placed about 1 inch within the hair line and the nuchal point falls about 1½ inches within the scalp line. The epilating dose of 350 to 400 r at about 100 KVP unfiltered is delivered with care that the center of the beam is accurately perpendicular to the scalp at each of the five points nonhairy skin being adequately shielded (MacKee et al. ADS 53 458 1946). The hair loosens and begins to fall on about the seventeenth day. Its regrowth eventually has never disappointed me.

During the defluvium, abetted by manual epilation, energetic fungicidal therapy is employed. Buried and broken hairs may be encouraged to come out by a detergent grease such as Carbowax 1,500. Local rather than whole scalp epilation is not adequate and leads frequently to disappointment and trouble with relapses. Cure is controlled by careful examination in Wood's light. Isolated, stubborn fluorescent hairs may be picked out or removed by electrodesiccation, so hastening cure (Costello ADS 54 210 1946).

X ray epilation without any other treatment is dependably curative in my own experience and that of Lydon et al (BMJ 1 523 1949). I treat tinea capitis by epilation as soon as the parents allow me to. It is the most effective, and sometimes the only effective treatment for the disease (Eichenlaub and Osbourne MAnnDC 15 596 1946). The efficacy of x ray epilation was confirmed by reports of Cofano (Dermatologica 4 110, 1953) and Thorne and Orange (PostgradMedJ 30 423 1954). Partial epilations should *never* be done.

If Wood's light shows fluorescence and direct examination shows fungi and if epilation is done at once the head is bald at the end of 3 weeks, the child is cured in 6 weeks, and hair has regrown at the end of 12 weeks from the time the patient was first seen. I do not like procrastination.

Early reactions following x ray epilation are more likely to affect the apprehensive uncooperative child who can be prepared for the tiresome and somewhat alarming experience with a grain or two of Sodium Amytal. There often occur nausea, headache and slight fever some 1 hours after the x ray dose is given, but all such phenomena end within [illegible]4 hours. High voltage and filtration increase the immediate reactions both in percentage incidence and severity (Zugerman ADS 60: 722 1949). Graying of the hair at the time of its regrowth is occasionally noted (Zeligman ADS 66 627 1952). Previously straight hair has been known to grow back curly.

Roentgen epilation may be repeated probably with safety if the interval between the treatments is not less than 3 months. If a third epilation is performed, permanent damage and hair loss are expected (Hazen ADS 56 539 1947). There is of course no hazard to the child's brain, regarding which the parents frequently require reassurance.

Epilating Wax. A good one is made of beeswax, 1 part by weight, and powdered rosin 4 parts (Pusey J 87 665, 1926). The first is melted and the second added with stirring. While warm, the wax is smeared thick on muslin, the strips are applied to the clipped scalp, the wax is allowed to cool and the muslin strips are jerked off the child's head against the grain, removing all hair cleanly (Davidson et al. CanadMAJ 30: 620 1934).

Thallium Epilation. Thallium acetate, a deadly poison in overdosage, may be given by mouth to loosen hair and cause temporary epilation in the treatment of tinea capitis. The drug must not be administered to a patient older than 11 years. A single dose is given and it may not be repeated for several months. The dose is meticulously calculated at 8.5 mg per kg body weight. This dose accurately weighed and the weight most carefully checked, is swallowed by the child with milk at a meal. Hair begins to fall about 13 days later, can be epilated with adhesive tape or epilating wax during the next few days, and generally begins to grow back in about 25 days.

Thallium poisoning has been fatal, most fatalities having resulted from overdosage usually from the careless handling of decimal points in the calculation. Such misad-

venture i abhorrent as well as preventable It appears that BAL, given as for any heavy metal poisoning, is effective in thallium poisoning Perhaps iodide by mouth would serve as an antidote for thallium iodide is extremely insoluble See Dermatitis medicamentosa.

ESTROGENIC SUBSTANCES loosen the hair Dobes (AD 7 : 32 1935) told me He found Amniotin especially suitable giving children under 5 years of age 10,000 units weekly for 4 to 6 weekly doses, and children over 5 years 20,000 units. When the hair loosened, he applied collodion to the areas, and this enabled him to pull out the infected hairs without breaking them off

KERION OF THE SCALP —This heals spontaneously Manual epilation helps. One must patiently temporize using gentle measures for simple cleanliness. No medicines help the condition. Rarely an abscess develops under the lesion and requires incision and drainage Some scarring with partial alopecia, is likely to result. Kerion development is not preventable It takes two months or more to heal. It is erroneous to overtreat, over irradiate or incise but correct handling is regularly followed by regrowth of hair and little or no cicatricial alopecia (Keim pers. comm., 1955)

TINEA CAPITIS.—See Lario (ADS 18: 119, 1939), thallium; Buschke (DZtsch 77: 186, 1938) thallium, Poth and Kaliski (ADS 45 121 1942) estrogenic substances given to change susceptibility of host Miller et al. (J 132 67 1946) M audouini cases cured probably by manual epilation rather than any fungicide tried; Carrick (J 131 1189, 1946) copper oleate and fatty acid derivatives second choice when x-ray epilation not available for M audouini cases; Montgomery (JID 9 1, 1947) facilitate electrolysis of isolated hairs under Wood light with fluorescent eosin, shellac, alcohol solution Combes and Lehrman (ADS 57 74, 1948) epilating dose 350 accidentally applied twice to one patient without harm F isher (ADS 56 55, 1948), salicylanilide therapy technic cure in average of 6 months Behling and Markel (JID 11 239 1948) Elkhart epidemic 5,400 school children, cured 78% in a year with topical applications; Scully et al. (JID 10 111 1948), inflammatory reactions associated with high cure rate; Rankin et al (SouthMJ 44: 615, 1951) Sporgen effective; Kligman and Anderson (JID 16 155, 1951) M audouini cures good with ointment base as with zinc ethylene bis-dithiocarbamate; La (ADS 64 384 1951), spontaneous cures; Reiss and Doherty (J 147 228, 1951) podophyllum treatment Schwebel et al. (J 149 281 1952) podophyllum worthless in M audouini cases.

THE BLASTOMYCOSES

The blastomycoses are chronic infectious diseases due to budding fungi. These occasionally attack the skin giving rise to purplish, moist, papillomatous lesions, and sometimes invade internal organs and subcutaneous tissues, giving rise to granulomatous tumors. Histologic features of the mycotic granulomas were reviewed by Moore (JID 6 149 1945)

Mycologically Swartz advised me that correctly blastomycetes are yeast like fungi which bud both in lesions and in cultures, including *Cryptococcus neoformans* (*Torula histolytica* producing European blastomycosis), *Candida albicans* and *Pityrosporum ovale* but excluding *Coccidioides immitis Paracoccidioides brasiliensis Blastomyces dermatitidis* and *Histoplasma capsulatum* because, while these produce budding in lesions, they grow moldlike on all media at room temperature.

Criteria were given by Schwarz and Baum (AD 71 143 1955) for distinguishing between true primary infections and the more usual manifestations of deep fungus infections. Primary cutaneous mycoses are characterized by (1) a definite history of the trauma which allowed inoculation to occur and was followed by the development at that site of a solitary chancre within a few days or weeks (2) evidence favoring the probability that the inoculating trauma involved actual contamination with the infecting fungus (3) development of lymphangiitis and regional lymphadenitis, so that the chancre and these phenomena together comprise a primary complex (4) proof of absence of previous pulmonary mycosis by historical clinical serologic and roentgenologic evidence and (5) change of skin reactivity from negative to positive along with, perhaps the finding that the serologic titer rises. Secondary skin lesions, stated Schwarz and Baum often are multiple, are not contemporary and are progressive Regional lymphangiitis and lymphadenitis are not likely unless secondary infection occurs. Pulmonary disease can generally be found if it is carefully sought Skin reactivity that was positive may become negative Serologic response may show increasing titer if the disease is progressive

THE BLASTOMYCOSES AFTER MOORE (ADS 38: 163, 1938)

DISEASE	FUNGI	CLINICAL CHARACTERISTICS	FUNGUS IN TISSUE OR PUS	CULTURE, GROSS	CULTURE, MICROSCOPIC
Coccidioidal granuloma	*Coccidioides immitis*	Infectious granuloma, acute, subacute or chronic. Cutaneous, subcutaneous, or systemic lesions. Lesions may be nodular, ulcerative, papillomatous, verrucoid, gummatous	Cells isolated or in giant cells, spherical, thick walled, diameter 3–80μ, reproduce by endospore formation, budding absent	Colonies flat, somewhat submerged, grayish, becoming white to light cream, with aerial hyphae cottony, at times coremioid, growth rapid	Hyphae septate, branching, 0.5–4μ in diameter; arthrosporous cells 2.5–7μ by 5–12μ; chlamydospores abundant, 6–8μ in diameter; racquet mycelium, terminal hypnospores [illegible] × [illegible]μ; anaerobic endogenous spore formation.
North American blastomycosis	*Blastomyces dermatitidis*, *Zymonema gilchristi*, *Zymonema capsulatum*, *umbellatum*	Infectious condition, often granulomatous. Cutaneous or systemic lesions. Cutaneous lesions primary or secondary, papulo-ulcerative, verrucous or papillomatous, gummatous	Single or budding yeastlike cells, thick walled, 5–20μ in diameter, usually approximately 7μ	Colonies at first yeastlike, then coremioid, finally profuse and cottony, changing from white to cinnamon; radiating ridges and concentric rings of growth. *B. capsulatum* remains white	Hyphae septate, branching, 2–4μ in diameter; conidia pyriform or round, pedicellate or sessile, 5μ in diameter; racquet mycelium, 5–6 × 3.5μ; chlamydospores terminal or lateral, 5.5–7.5 × 13–15μ; ascogenous cells spherical, 5–13μ.
European blastomycosis	*Cryptococcus neoformans*, *Atelosaccharomyces busse-buschkei*, *hominis*	Similar to No. Am. blastomycosis but ulcerative in cutaneous form, with abscesses, little inflammation; in addition cerebrospinal system	Thick walled, heavily encapsulated, simple or budding cells approximately 5–10μ, occasionally larger	Colonies yeasty or pasty, smooth, mucoid to moist, subpultinate; color light cream, becoming light tan to brown with age; growth fair	Spherical to ovoid budding, encapsulated cells approximately 3–8μ in diameter, rarely larger; no mycelium, pseudomycelium or spores.
South American blastomycosis, Paracoccidioidal granuloma: A. Generalized; B. Localized affecting buccal mucosa	(a) *Paracoccidioides brasiliensis*; (b) *Paracoccidioides tenuis*; (c) *P. cerebriformis*	A. Generalized or localized, cutaneous or systemic, granulomatous, papular, verrucous or ulcerative, acute to chronic, usually spreading in lymphatics. B. Lesions localized on buccal mucosa; acute to chronic; verrucous, papillomatous, ulcerative, granulomatous, spreading in lymphatics only in terminal stage	(a) and (b) Cells spherical or ovoid, 1–30μ in diameter, thick walls, simple or multiple budding of minute, spherical, ovoid or bacillary gemmules. (c) Cells spherical or ovoid, 3–30μ in diameter, larger than those of *P. brasiliensis* or *P. tenuis*, thick walled, with simple or multiple budding of small, spherical, ovoid or elongated gemmules	(a) White, adherent to substratum and somewhat hard, well-defined, somewhat cottony. (b) Mycelium mostly submerged; colonies compact, verrucoid or vermiculate at inoculation, showing folds or radiating ridges; white; growth slow. (c) On gl. cerebriform to vermiculate, yeastlike, creamy buff, becoming light cinnamon-buff with age, easily separated from substratum, but filamentous, flat and adherent to dry portions of substratum; growth slow	(a) Hyphae septate, branching, 1.5–3.5μ, hyphal swellings 3–6μ, spherical, terminal chlamydospores to 15μ; conidia lateral, small or pedicellate, 3–7μ. (b) Same as *P. brasiliensis*, corresponding structures smaller. (c) Hyphae irregularly septate, branching, 2–7μ with many swellings; cell arthrosporous, oidioid, dumbbell-shaped; chlamydospores spherical, elongate, pyriform or sclerotia, intercalary, lateral or terminal, up to 15μ.

BLASTOMYCOSIS OF GILCHRIST (NORTH AMERICAN BLASTOMYCOSIS)

Blastomyces dermatitidis is the causative parasite. Infection may begin on some exposed surface, with a small papulopustule which gradually enlarges. Crusting is present almost from the beginning The underlying lesion comes to consist of reddish or purplish, irregular papillomatous tumors bathed in seropurulent fluid. The patches tend to extend peripherally and heal in the center with atrophic scarring

Primary cutaneous blastomycosis, which is rare is exemplified by the patients reported by Wilson et al. (AD 71 39 1955) They developed after infection from a proven source primary chancriform lesions accompanied by lymphangitis and lymphadenitis. They did not develop the cutaneous form of blastomycosis characterized by slowly enlarging plaques of ver



Fig. 677 —Blastomycosis of Gilchrist. (Dr Grover Wende.)



Fig. 678.—Blastomycosis of Gilchrist. (Dr John Butler)



Fig 679.—Blastomycosis. (Dr J B. Kessler)



Fig 680 —Blastomycosis. (Dr F B. Wright.)



Fig 681.—Blastomycosis. (Dr J W Perkins.)

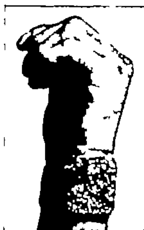


Fig 682.—Blastomycosis unusual bracelet like lesion of wrist. (Dr H. D. Michelson.)



Fig. 683.—Blastomycosis in an infant. (Dr J H. Kessler.)



Fig. 684.—Blastomycosis in an infant. (Dr J H. Kessler.)





Fig 685.—Blastomycosis in a farmer from Minnesota. (Dr John Butler.)



Fig. 686.—Blastomycosis of groin.



Fig. 687—Blastomyces in abscess.

Fig. 688.—Blastomycosis, productive of extensive scarring of wrist and hand.
Fig. 689—Blastomycosis. (Dr J. Lamar Calloway)

rucous, pustular dermatitis that is not accompanied by lymphadenopathy They were infected by pathology laboratory work 3 while performing au topsies and 1 while cultivating the organisms.

Cutaneous blastomycosis must be distinguished from tuberculosis verru cosa, sporotrichosis, vegetating syphilids, and bromide eruptions. The demon stration of the organisms, directly in biopsies or by culture is necessary for positive identification of the infection. The pus from microabscesses, transferred to a slide into water not KOH and examined with a narrow pencil of light may be seen to contain the singly budding yeastlike cells which are from 5 to 20 μ in diameter (Nomland ADS 32 924 1935)

Histologically the skin lesion shows remarkable pseudoepitheliomatous hyperplasia. Enlarged and deformed dermal papillae are the seat of chronic, purulent, granulomatous inflammation. *In the plane section of the tissue, this is found within papillomatous* epithelium as microabscesses. The budding *fungi* can be found in the dermal inflammatory tissue fairly easily as a rule. *B dermatitidis* cells are double-contoured and lack the capsule formed by Cryptococcus (Torula)





Fig 690 —Blastomycosis of *Gilchrist.* (*Dr Otto L. Castle.*)
Fig 691 —Blastomycosis histologic structure, showing papillary abscesses and pseudo-epitheliomatous hyperplasia. (*Dr F W Shaw*)

The disease is more often pulmonary in inception than dermal according to Schwartz and Baum (AmJClinPath 1 900 1931) who reviewed 22 Cincinnati cases and 36 from the Armed Forces Institute of Pathology The tendency in the lungs is to heal, but the disease extends via the blood and lymphatic system as well as by peripheral invasion. In active pulmonary disease there is always destruction of the mucosa of the smaller bronchi, while cavities are uncommon and pleuritis is always present usually dry and fibrinous Cutaneous blastomycosis is generally secondary to primary pulmonary infection and the disease appears to be transmitted by way of the respiratory tract Schwartz and Baum believed. That blastomycosis is not a local cutaneous disease but rather a systemic one was indicated by Ormsby and Miller (JCutDis 1 1903) whose photomicrographs showed internal budding only suggestive of (Coccidioides immitis). See Ormsby (ADS 39: 1069 1939)

An epidemic of North American blastomycosis, carefully documented, involved 10 patients in a small southern community studied by Smith et al. (J 159: 641 1955). Erythema nodosum not previously reported as occurring in this disease was observed in 3 cases. Examination of gastric washings was found helpful in diagnosis. Epidemiologic studies by Schwartz and Goldman (AD 1 84, 1956) disclosed 100 cases in 1953, located mainly in the central and southeastern parts of the United States a few in Wisconsin; there were 3 deaths.

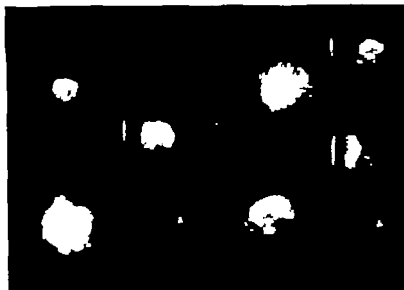


Fig. 692.—Culture of *B. dermatitidis* at 10 days in glucose agar except in the tube on the right, which is conservation medium. Note moist peripheral zone. (Dr. Fred Weidman.)

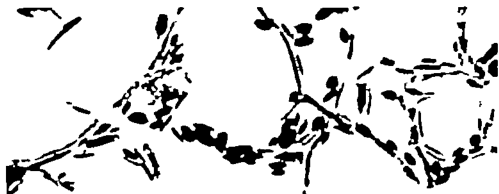


Fig. 693.—*B. dermatitidis* from culture. (Dr. F. W. Shaw.)

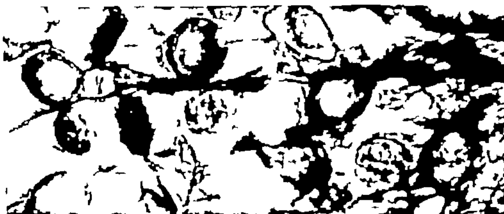


Fig. 694.—*B. dermatitidis* mass from experimental peritonitis of mouse. (Dr. E. Muskatblit.)

Most of the localized infections do not endanger life and respond fairly promptly to appropriate treatment. Scarring usually results. The possibility of systemic dissemination is always present, and systemic infections are serious. A young man with forehead lesions, for example developed meningitis, and autopsy revealed multiple abscesses including several in the central nervous system (Franks and Taylor ADS 48 88 1943) The mortality was 92% in systemic cases followed 2 years or more by Martin and Smith (AmRevTubere 39 275, 488 1939) in their review of 360 cases, with an extensive bibliography This has changed remarkably since the stilbene derivatives were introduced in therapy

Immunologic aspects were studied by Peck et al. (JImmunol 38: 449 1940) who found 2 polysaccharides which fixed complement of immunized rabbits and provoked tuberculin type reactions on intradermal injection in sensitive individuals, who could be hyposensitized. A complement fixation test was positive and appeared to be specific in 8 systemic cases of Martin (JInfectDis 57: 291 1935) Specific allergy was demonstrated in experimental infected guinea pigs by Nelson (JID 5: 257 1943) Skin tests with blastomycin yielded negative results when tried on persons exposed to the infection, reported Schwartz and Baum (JID 18 1, 1952)





Fig. 495.—Blastomycosis tiny abscesses surrounded by epithelium. Several fungus cells can be seen (Dr Fred Weidman)

Fig 496.—Blastomycosis fungus cell within a giant cell. One is budding. (Dr Fred Weidman)

Treatment.—Local, papillomatous lesions can be expected to respond favorably to tincture of iodine solid carbon dioxide or electrosurgical destruction. Roentgen therapy is valuable given in doses of perhaps 200 r weekly sufficient to achieve atrophy of the granulomatous process. Internally iodides in large doses used to be given. Sulfonamides in high concentration inhibited cultures (Noojin and Callaway ADS 47 620 1943) but they did not benefit a patient of Sayer (BullUSAMD 43 333 1942) nor did penicillin although huge doses of iodides did.

Stilbamidine and Related Chemotherapeutic Agents.—Aromatic diamidines were synthesized by Ashley et al (JChemSoc, 1942, p. 103) in their search for trypanocidal drugs.

Propamidine (4 4-diamidinodiph o lo propan hydrochlorid) wa found b Elso (JInfect Dis 76 193, 1945) t be effecti f gist t e *fo B dermat tidis* in a dilution of less than 0.5 mg pe 100 cc aga The drug was tried by Corbert et l (JID 14 71, 1950) whose preliminary report was encouraging The therapeutic potentialities of several

aromatic diamidines were investigated by Schoenbach and Greenspan (Med. 2 : 327 1948) but their work with stilbamidine (4,4-stilbenedicarboxyamidine) did not include its mycologic significance Steroid hormones were investigated with respect to fungistasis by Reiss (ADS 59 403 1949) who found diethylstilbestrol the most effective but *B dermatitidis* was not investigated, and their effect on *C. albicans* and *T histolytica* was nil. Schoenbach et al. (J 146: 1317 1951) used propamidine and stilbamidine in cases of systemic blastomycosis with remarkable results. Curtis and Harrell (ADS 66: 676, 1952) reported experimental studies of the fungistatic action of stilbamidine and several related substances with respect to *B dermatitidis* and they cured cases of blastomycosis with it. Two of their 4 were of the localized type in elderly men who were treated at the University of Virginia Hospital for inoperable cancer of the prostate with diethylstilbestrol. The coincidental response of their fungus infections was noted, and of them they were cured. The other 2 patients had systemic blastomycosis and were treated with stilbamidine which was selected as being the most promising of the group of drugs and without gonadotropic effects. They were cured. Fink et al. (J 151: 1393, 1953) also cured such a patient and . m re critically ill with the systemic disease were cured by Slaughter (ADS 70: 663, 1954) While the noteworthy effectiveness of these drugs is now common knowledge, blastomycosis has by no mean been conquered, as shown by the experience of Sutliff et al. (AnnIntM 41: 89 1954) of whose 15 cases from Memphis, 2 of the 7 treated with stilbamidine proved refractory

The dose of stilbamidine approximates 150 mg dissolved in 250 cc. of saline or 5% glucose and given slowly in from 1 to 3 hours, intravenously daily for 3 weeks, followed by a rest period of 10 days and a repetition of the course The total dose required ranges from 4.5 to 6 0 Gm. or more, and toxic effects from such dosage are not unusual. The drug may produce destructive lesions of the liver or kidneys, fatal 3 or 4 months after the last injection. More likely it may damage the trigeminal nerve producing within from 1 to 5 months after the end of treatment numbness of the central region of the face. The dosage and effects were reviewed by Smith (GP 8 69 1953) who emphasized the fact discovered by Schoenbach *et al.* (AnnIntM 37 31 1952) that the drug *must* be protected from exposure to sunlight in order to prevent its becoming toxic Hepatic or renal toxicity has not resulted from treatment with fresh solutions, according to Miller (J 152 184, 1953)

Stilbamidine is not the preferred agent for treating local skin infections, which can be cured with iodides, x ray therapy and surgery Efforts to find equally effective drugs of less inherent hazard are being energetically pursued, but sensory neuritis must be assessed as a price worth paying fo cure of an otherwise fatal infection. The fungistatic activity of stilbamidine and several related chemicals wa reviewed and investigated by Bocobo et al. (JID 21: 149, 1953) who observed that the pathogenic fungi sensitive to these substances included *B dermatitidis B brasiliensis, H capsulatum S schenkii* and *C. immitis.*

Baxvan and I (unpublished) tried stilbamidine isothionate topically in a vanishing cream base on superficial dermatomycoses, with largely disappointing results. In vitro tests suggested the drug might be effective against *T rubrum M gypseum, E. floccosum, M audouini,* and *T schoenleini,* for these did not grow in mediums to which 1 mg./ml. stilbamidine isothionate had been added. *C. albicans* was insensitive.

See Gilchrist (JohnsHopkHospRpts 1 269, 1896; BMJ 2: 1321, 1902) New and Childrey (AOtol 12: 134, 1930) primary of tongue; Redaelli and Ciferri (JTropM 37: 280, 1934) mycology; DeMonbreun (ADS 31 831, 1935), fatal case; Hamblen et al. (AmJObGyn 30 345, 1935) uterus and tubes involved Hsuh (ADS 43 465, 1941) generalized case helped with iodide; Smith (J 116 200, 1941) diagnosis; Hitch (JID 5: 4) 1942) gentian violet no help although effective in vitro; Feshay and Madden (AmJTropM 22 665, 1942) systemic infection of dog; Jones and Martin (Surg 10 931 1941), unusual osseous case Albert (BJD 56 294 1941) cure with sulfonamide; VanDellen (JInfectDis 76 47 1945) antibiotic from *Chromobacterium violaceum* inhibits *B dermatitidis* Cassady (AOphth 35 84 1946), uveal involvement Levine and Ordal (JBact 52 687, 1946), mycology Brody (ADS 56 529 1947) pulmonary and subcutaneous Starrs and Klotz (AIntM 82 1 29 1948) review; DeLamater (JID 12, 101, 1949) mycologic ariation Manwaring (APath 48: 421, 1949) unusual forms in tissues; Noojin and Praytor (J 147: 740 1951) newborn of infected mother carried complement-fixing antibodies for 3 months although itself uninfected Busehmer (JThoracicSurg 25 468, 1953) pulmonary resection appropriat in 3 cases; Marshak and Rodriguez (ADS 68 94, 95, 1953), 3 stilbamidine cures Parker et l. (J 153 129 1953) stilbamidine cured systemic case, Williams and Klemptner (J 153 840, 1953) patient with tuberculosis and blastomycosis cured of latter with no harm to former by iodides, streptomycin and stilbamidine Edit (J 154 532, 1954) 2 hydroxystilbamidine less toxic than some aromatic diamidines, encouraging in cases of Snapper and McV y (AmJMed 15: 603, 1953) useful in actinomycosis (Miller et l.; J 150 35, 1952) and sporotrichosis (Harrell et al. AI tM 93 162, 1954)

COCCIDIOIDOMYCOSIS

Infection with *Coccidioides immitis* apparently is commonly acquired by way of the respiratory tract through inhalation of spores; this is a hazard to laboratory workers with cultures of the fungus (Looney and Stein: NEngJM

242 77 1950) Endemic foci exist in California (San Joaquin Valley) Arizona, Mexico New Mexico and Western Texas (Burks and Thompson South MJ 39 613 1946) The skin test, negative on arrival, frequently becomes positive in personnel introduced into such regions (Lee CalifWM 61 133





Fig. 697—Coccidioidal granuloma, nodulo-ulcerative lesions of face. (Dr Werner Duemling)

Fig. 698.—Close-up of left cheek lesion of Fig. 697 (Duemling ADS 60 781 1949.)



Fig 699—Cutaneous lesions of coccidioidomycosis. (Dr William Allen Pusey)

1944) although such primary infection may be asymptomatic or manifested only by what would pass for influenza (Dickson AIntM 59 1029 1937) Such manifestations are often accompanied by erythema nodosum from which most patients recover without complication (Dickson J 111 1362, 1938 AmRevTubere 38 711 1938) Of 1,351 infections reviewed by Smith et al.

(AmJPubH 38 1394 1946) 60% were without symptoms and only 25% were clinically manifest. Erythema nodosum occurred in 4.6% and dissemination in only 0.25% mostly affecting Negro males. Progressive disease is analogous to the overwhelming tuberculosis of childhood. Features of pulmonary x rays range from a small nodular opacity through exudative but clearing lesions to nodular densities which may eventually calcify according to Winn and Johnson (AnnIntM 17 407 1942)

Primary cutaneous infections occur While most infected perso s recove some suffer progressive disease. Acute dissemi ting primary coccidioidomycosis is almost always fatal in from 1 to 6 months. Chronic disseminating disease coccidioidal granuloma, h a mortality f about 50% Gen rali ation m y follow sk o pulmo ic primary disease presumably via the blood stream.

In miliary coccidioidal granuloma the lesions are found preferentially located on the head neck, shoulders nd upper extremities (Epstein ADS 38: 75_, 1938) They are verrucose and papillomatous. They involve mainly the kin and occasionally the mucosae. Morbilliform ra hes h ve been n ted (Gol lstein an l MoDo 11: J 1 4: 637 1944) Fe er is usual and visceral involveme t follows. The organisms are easily demonstrated.



Fig. 160.—*Coccidioides immitis* in pus. These cells had internally are much larger than those of blastomycosis, and can be seen easily under low magnification. (Dr F D. Weidman.)



Fig. 161.—Endosporulating spherule of *C immitis* in tissue. (Dr Werner Duemling.)

In chronic coccidioidal granuloma, typicall affected re the sternoclavicular joints, the neck, th sides of the feet, and the ingui al regions. The lesions are furunculoid granulomatou becomes. The connective tissues of deep structures re mainly involved a d th mucosae are ffected only rarely The course is low with remissions and relapses. Fever is low or bse t. The viscera are involved to a lesser extent, the organism are more d fficult to demonstrate nd the outlook is better th in the miliary type of case Arthriti involvem t o symptom suggesti g Pott disease, appendic tis or pneumonia may confuse the diagnosis (Rosenberg et al. AInt M 69 238, 1942 Quill and Burch A aRurg 120 670 1944)

Diagnosi depends on demonstration of the organisms, directly in tissues o by culture. A kin test, us ng a vacc nal preparation of *C. immitis* as the antigen, is highly specif (Kessel AmJTropDi 19 199 1939) but reactivity persist long after activity of the disease may ha e faded.

The struct re of cocc dioidal gran loma that of the infectious granulomas, the ca sative organism be g fou d generally w th the gia t cells of the exudat (Wiseri ADS 61: 1010, 1950) They multiply by e dog ous f rmation of spores. In the pus they are doubly contoured sph res 5 to 60 μ in d ameter with granula protoplasm. In iso-

tonic saline, sealed under a coverglass, they quickly germinate a septate mycelium (Wilson: ADS 5 : 561 1948) They grow on dextrose agar The organism has been found in the soil at the place where infection occurred (Davis et al.: J 118 1182, 1942) Dust control by grassing, paving and application of oil has reduced the rate of infection (Smith et al.: J 132 833 1946)

Treatment with potassium iodide has little effect on the course of the disease Antimony and potassium tartrate and roentgen therapy have been used with benefit. Coccidioidin, a vaccinal preparation, has value (Jacobson ADS 40 521, 1939 57 561 1948) Doses must be of proper size and timing to immunize Incision and drainage should not be performed. Thymol in doses as great as 6 Gm. daily may help (Sox and Dickson J 106 777 1936) Penicillin is ineffectual (Arnold and Levy SouthMJ 39 609 1946) The value of stilbamidine and related drugs (see Blastomycosis, treatment) remains to be discovered. Diethylstilbestrol failed in 2 cases of Piper and Goldblum (ADS 70 809 1954)

See Childrey and Grey (CalifWM 37 248, 1932) primary in nasopharynx Sorsky and Kroon (CalifWM 42 98, 1935) differentiation from tuberculosis Duckett and Fredeen (JKansMS 36 111, 1936) fatal meningitis in infant, cause of hydrocephalus Jordan and Weidman (ADS 33 : 31 1936) comparat mycology Dickson (CalifWM 47 151, 1937) "Valley Fever" Hurwitz et al. (CalifWM 48 87 1938), coccidioidin skin test Stewart and Meyer (JInfectDis 63 196, 1938) mycologic features, resistance to desiccation Hynes (KoWMed 25 19, 1939) sulfonamide beneficial Gilfillan (J 112 1233, 1939), osteomyelitis Foley et al. (WestJSurg 48 738, 1940), periostitis of skull, case helped with thymol; Farness (J 116 1749 1941) review, Smith (TexasSJM 33 333 1942) Texas cases, diagnosis; Smith (Radiol 38 643, 1942) parallelism with t berculosis, Aronson and Gallagher (AmJPubH 32 636, 1942) coccidioidin, Stiles and Davis (J 119 765, 1942) features of disease in man and animals Willett and Weiss (AnnIntM 23 349 1945) endemic area bounded by Needles, Banning and Tempe; DeLamat and Weed (PSEMIC 21 505, 1946), budding forms in tissues Rosenthal and Routien (Sci 104 479, 1946, AIntM 80 343 194) infectivity of spherules proved by inoculation, Clark (RockyMtMJ 44 202, 1947) roentgenographic changes in chest, Kurz and Loud (NEngJM 237 710 1947) East Coast cases Smale and Birsner (J 140 1152, 1949) 3 infants, uninfected, carried positive complement fixation antibodies of diminishing titer from maternal infections which proved fatal to mothers Duemling (ADS 60 781 1949) cases Greer et al. (JThoracicSurg 18 591 1949) excision of lung lesions Melick (JThoracicSurg 20 66, 1950) lung surgery perience Georg et al. (Sci 114 387 1951) selecti e medium utilizing actidion 0.1 mg/cc., inhibiting fungi other than C immitis Dykes et al. (AmJDisChild 85 34, 1953) osseous in children.

PARACOCCIDIOIDAL GRANULOMA (SOUTH AMERICAN BLASTOMYCOSIS DE ALMEIDA'S DISEASE)

Paracoccidioidal granuloma is a chronic granulomatous disease caused by *Paracoccidioides brasiliensis P tenuis* or *P cerebriformis* which may affect the skin mucosae lymph nodes and viscera (Moore ADS 38 163 193 see also Conant et al. Manual of Clinical Mycology Saunders, 1944) Localized lymphangiitic disseminated and mixed types of cases are described The generalized disease may be acute or chronic. The fungus may enter the buccal tissues, forming a hard infiltration of the gums, spreading to the lips, nose and margin of the tongue Affecting the skin primarily a lesion may develop upon an abrasion where the fungi have become lodged. *P brasiliensis* was found in a dental granuloma in a woman who also had lymphatic lesions by Bogliolo (ADS 61 470 1950) who thought the infection capable of commencing in periodontal tissues and spreading via the lymphatics so as to simulate Hodgkin s disease Paracoccidioidomycosis shows a marked predilection to involve primarily the gastrointestinal tract including the oral and nasopharyngeal cavities while pulmonary involvement is common, perhaps by extension from the pharynx (Furtado et al. ADS 70 166 1954) Lymphoglandular cutaneous and generalized infections occur frequently but probably only secondarily to other types, stated Furtado et al who preferred *Aleurysma brasiliensis* as the name of the organism

Diagnosis depends on identification of the causative fungus (Jordan and Weidman ADS 33 31 1936) The organism listed as *Paracoccidioides brasiliensis* by Brumpt was first seen by Lutz in 1908

See de Almeida (AnnFacMed Sao Paulo 9 69 1933) Conant and Howell (PSExpBiol 46 426, 1941) Redaelli nd Ciferri (JTropM 37 280 1934) mycology F ri do and Pellegrino (be YBD 1948 p 81), 14 cases treated with sulfonamides, 4 died with disseminated disease, 3 unimproved, 4 helped, 2 much benefited, 1 cured) Perry et al (ADS 70 477 1954) suppressed benefit with sulfdiazine 1 case.

CHROMOBLASTOMYCOSIS

Chromoblastomycosis (Chromomycosis) is a polymorphous parasitic dermatosis, caused by *Hormodendrum pedrosoi*, *H. compactum* or *Phialophora verrucosa* productive of a primarily papular nodular or verrucose painless eruption which may progress with ulceration vegetation and hyperkeratosis. Verrucosities may be isolated or confluent, and may invade the whole foot or leg



Fig. 702.—Chromoblastomycosis of verrucose type, with central scarring. (Drs. V. Pardo-Castello, E. Rio Leon, and F. Trespalacios: ADS 45: 19 1942.)



Fig. 703.—Chromoblastomycosis of tuberculoid type, 2 years' duration. (Pardo-Castell et al. ADS 45: 19 1942.)

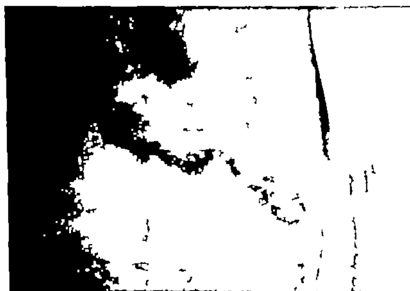


Fig. 704.—Chromoblastomycosis of the type resembling serpiginous syphilid. (Pardo-Castello et al. ADS 45 19, 1942.)

or other parts of the body Infection seems significantly often to follow injury with some form of wood and usually affects an exposed part unilaterally (Weidman and Rosenthal ADS 43 62, 1941)





Fig. 95.—*Blastomyces brasiliensis* in liver tissue. (Dr Edward A. Gall.)
Fig. 96.—*Blastomyces brasiliensis* showing multiple budding. (Dr I Muskatblit.)

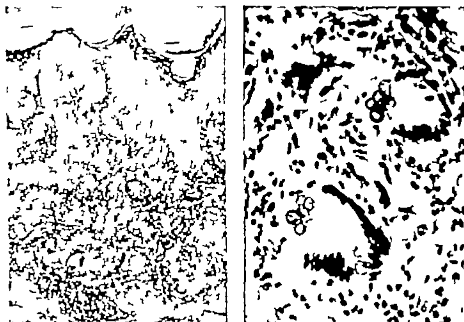


Fig. 97.—*Phialophora verrucosa* (Drs. Morris Moore, Zola Coope and Richard Weiss J 172 123 1943.)

The disease was apparentl first mentioned by Pedroso Bra il in 1911 but wa not publ hed t l 1920 wh w th Gomes Pedroso reported 4 c ses accord g t Moore (ADS 40 124 1939) The first case ctually described i a journ l rticle wa that of Lane (JCutDi 33 840 1915) in whose 19 ear-ol l Itali m le patient th lesion wa a abscess on the buttock St l ing th fu gus btained b culture from thi Medlar (J MedRes 32: 30 1915) fou l P ucosa

Cli leally Moore co tinued, chromomycosis i a ll a disease of the hands or feet. It m be papul r nodula erru oid or granulom tous, w th r w th t lcera tion and bsces f rm t on wi l w ll ell wi h brow A t pical lesion present

cauliflower like growths, some being pedunculated. There is usually no pain or lymphangitis. Microscopically the picture resembles closely that of tuberculosis, syphilis blastomycosis, a granuloma or a foreign body reaction. This is particularly evident in the decided hyperkeratosis, the acanthosis and some parakeratosis of the epidermis. In the corium there is marked edema with intense infiltration and fibrosis. This is made apparent by the granulomatous lesions with polymorphonuclear leukocytes, numerous lymphocytes, plasma cells, epithelioid cells, eosinophils, Russell f chsin bodies, macrophages, fibroblastic changes, discrete microabscesses and many giant cells of the Langhans or foreign body type confusing the picture with tuberculosis. Within these giant cells or distributed freely in the tissue may be seen the multilocular thick walled brown cells of the fungus, *P verrucosa*. These cells do not reproduce by budding but by transverse septum production which forms multilocular cells like mulberry clusters. Accordingly with the report f F P de Almeida and me (*Ann. M ssouri Botan Garden* 23: 543 1936) the name was changed from chromoblastomycosis given to the disease by O da Fonseca and A. E. de Arêa Leão (*Rev med cir d. Brasil* 6: 73, 1930), to chromomycosis. A number of fungi may produce the disease. These have different morphologic characteristics which seem to relate them to each other in phylogenetic sequence.



Figs. 708 and 709 —Chromomycosis showing acanthosis, dermal i filtration, and gia t cells. Higher magn fication reveals thick walled, brown cells of *Phialophora verrucosa* in the giant cells. (Moore et al. J 122 1237 1943)

The cases were classified clinically as verrucose, tuberculoid, syphiloid, psoriasiform cicatricial and elephantiasic by Lardo-Castello et al. (ADS 45 19 1942) who made their diagnoses by identifying the yellow brown round cells (sclerotia) in scales, pus and histologic sections where these are found in giant cells or small abscesses. While most cases occur on the extremities, a facial lesion simulating blastomycosis or verrucous tuberculosis was described by Moore and Mapother (ADS 41 42, 1940) who reviewed the literature. Mycetoma like lesions on the hand and wrist were reported by Emmons et al. (J 116 2_ 1941) and by Lewis et al. (JID 10 165 1948) whose patient was cured with x ray therapy and potassium iodide Surgical eradication or partial destruction combined with x ray therapy, is the usual necessity Iontophoresis with CuSo is among the therapeutic measures that have been recommended. Large doses of calciferol appeared beneficial in the 3 cases of Bonilla (ADS 70 665 1954)

See de Almeida (ArchdeBiol 20 68, 1936) Takahashi (bs ADS 37 514 1938) nodular and ulcerati case Kano (AfDuS 176 282, 1937) case, cheek Gomez (ADS 38 12, 1938) case, dorsum of hand d Fonseca (PrensaMed 48 132, 1940) taxonomy of Hormodendrum Carrión (Puert Rico JPubH 15, 340, 1940) mycology; Moore et l (J 122 1237, 1943) cases Binford et l (ADS 49 398, 1944), case chronic warty on leg; Snow et l (ADS 51; 99 1945) case, ankle Ansley (JID 8: 281, 1946) pathogenicity experiments; Berger et al.

(CanadMAJ 53: 132, 1945) Canadian case; Saxton et al. (MJAustral 1: 485, 1946), Queensland cases Calero (ADS 54: 285, 1946) 3 Panama cases Calero (ADS 57 266, 1948) case, leg and finger lesions; Mundt and Moore (NOrMJ 100 558, 1948) case and mycology, Carrión (ADS 61: 1002, 1950) mycology of Fonsecaea dermatitidis Kano Asulay (JID 19 39 1953) successful experimental human inoculation with F pedrosoi Conway and Berkeley (ADS 66 695, 1952) mycetoma due to H pedrosoi cured by plastic surgery Barrack (AustralJD 1: 207, 1952), Queensland cases, timber workers, uppe extremity usually; Powell (AustralJD 1 214 1952), Queensland cases, 17 due to F cladosporium 3 to F pedrosoi Barwasser (J 151: 866, 1953), case, wrist, histologic identification, cured by electrocoagulation Howles et al. (ADS 69 83 1954) 9 cases from Louisiana, where it is not rare.

MONILIASIS

Candida (Monilia) albicans (Zopf, 1890) identical with *Oidium albicans* (Ch Robin, 1853) is the type species of the genus Mycotorula (Will, 1916) as given by Brumpt. Colonies originate by bipolar sprouting of blastospores and the pseudomycelium is composed of ellipsoidal cells. The organism causes the development of a pellicle in liquid medium liquefies gelatin and ferments sugar The colonies are creamy thick and convex. Pseudomycelium is formed by short cells typically crowned by a verticil of blastospores. The terminal cell bears a bouquet of blastospores. Verticils are numerous, simple regularly spaced and globular at the end

C albicans is a yeastlike' fungus differing from a true yeast in that a pseudomycelium is formed, whereas true yeasts reproduce by budding, and the daughter cells do not adhere to the mother cell. This fungus and others closely related to it cause many different kinds of clinical manifestations, which may be localized, widespread or scattered, acute or chronic inflammatory or indolent They are capable of infecting skin its appendages, mucous membranes, and gastrointestinal tract and other viscera singly or in combination. Some strains in persons are potent sensitizers, capable of provoking eczematous sensitization as well as passively transferable antibodies They are often found behaving as saprophytes, and the factors which influence pathogenicity are ill understood. When one has found monilia, one has not *necessarily elucidated the cause of the disease under investigation.*

Clinical Forms of Moniliasis (Lewis and Hopper NYSJM 38 899 1938; see also Shelmire ADS 12 789 1925 Belisario MJAustral 2 538 1934; Ormsby MichSMSJ 37 135 1938) are as follows

LOCALIZED

Onychia and paronychia
Intertrigo (axillary submammary inguinal)
Erosio interdigitalis blastomycetica (essentially a variety of intertrigo)
Perlèche (essentially a variety of intertrigo)
Superficial glossitis
Stomatitis (thrush)
Localized eczema
Water bed dermatitis
Vulvovaginitis (with or without symptoms)
Gastroenteritis (with or without symptoms)

GENERALIZED

Widespread eruptions usually associated with some of the localized forms. Characteristic flat pustules may usually be observed in some part of the eruption. These pustules become dry and macerated scales form on the surface. With exfoliation, a bright red, moist surface is left with overhanging edges Sparse growth of hair may be an additional finding

Moniliids in which no fungi can be cultured and which are secondary to a focus of infection with C albicans. Pompholyx may be a moniliid

SYSTEMIC

This group includes cases of pulmonary involvement and massive gastrointestinal infection. Such infections are often associated with cutaneous infection and have proved incurable.

Monilial Onychomycosis.—The organisms may inhabit the nail plate, where they produce disease indistinguishable on clinical grounds from other kinds of onychomycosis (q v p 491)

Monilial Paronychia.—See Tinea mycotic paronychia (p 495)

Monilial Intertrigo.—Intertrigo is a clinical name applied to any superficial dermatitis characterized by redness abrasion and maceration, occurring on opposing surfaces. *Hyperhidrosis is followed by fermentation,* and the

skin becomes abraded and raw The gluteal and cruroscrotal folds, the infra mammary region and the folds of the neck are common locations. Hot weather obesity and binding garments are predisposing factors. Monilia are the or ganisms usually to blame although streptococci or staphylococci may be the

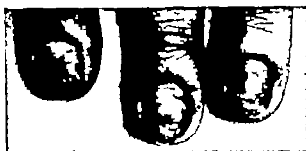


Fig. 710.—Monilial onychomycosis. (Dr W Herbert Brown.)



Fig. 711.—Monilial intertrigo.

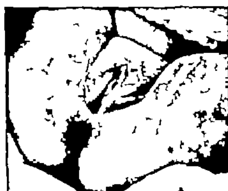


Fig. 712.—Monilial vulvitis in an infant



Fig. 713.—Perlèche. (Dr R. M. Montgomery.)



Fig. 714.—Monilial interdigital dermatitis in a laundress. (Dr James H. Mitchell.)

infecting agents. Monilial intertrigo sometimes represents the result simply of luxuriation of pathogenic flora of the skin the flora including pathogens usually because of the existence of foci of infection. Obese women are the commonest sufferers because of their monilial vaginitis, the presence of yeast like organisms in the vagina being a common circumstance

Monilial folliculitis is not an unusual concomitant of intertrigo especially when this has been treated with an ineffectual ointment (Sylvest ActaD-V 28 201 1948)

In prophylaxis, simple cleanliness and dryness are preventative achieved by loose clothing, good ventilation and the use of bland dusting powder Exertion in hot moist weather almost inevitably leads to trouble particularly in fleshy persons and fat babies. Focal infections and sources of reinfection must be controlled. Wet packs are excellent using cool 1 500 aluminum acetate in water or 1 10 000 bichloride of mercury The parts should be dried, perhaps swabbed with 10% aqueous solution of silver nitrate and dusted generously with borated talc. Often it is desirable to immerse the whole body in medicated baths, and potassium permanganate 50 grains to 15 gallons of cool water is effective Ointment preparations meet with little success although 2% sulfur in Vioform Cream is often helpful. AVC cream or Propiongel may be effectual, along with gentle cleansing with water daily

Monilial Interdigital Dermatitis.— Erosio interdigitalis blastomycetica was one name early given this condition when the organisms seen in smears were misinterpreted as nonmycelial blastomyces. The disorder involves one or both hands and usually appears on the web between the middle and ring fingers. Women, especially laundresses are particularly susceptible (White ADS 16 401 1927) A pudgy configuration of the hand abets the infection by keeping the interdigital web region moist and ill ventilated. The lesions are superficial, inflammatory and sharply defined, and have slightly undermined macerated borders, from beneath which the organism can be obtained and cultivated Extension over the dorsum of the hand and up the forearm is not rare. Diagnosis may be confirmed by KOH preparations and cultures. The disease is resistant to treatment but dryness, débridement and repeated applications of alcoholic solution of gentian violet (Cornbleet ADS 20 184 1929) or 3% chrysarobin in chloroform or Castellani's paint (Seale and Clark SouthMJ 41 627 1948) will usually succeed. Effort must be made to prevent contact with irritating chemical substances, and nutrition should be optimum Vioform Cream with the addition of 3% sulfur is often beneficial

Monilial Stomatitis.—Oral lesions associated with *C albicans* are thrush, glossitis and perlèche

THRUSH is manifest as superficial adherent deposits resembling coagulated milk The lesions bleed if the membrane is forcibly removed The mucosae of the tongue cheeks and pharynx are the sites of predilection. The circumoral skin may be involved *Pityriasis alba* is the name applied to furfuraceous scaling seen about the mouth in children who have oral moniliasis or perhaps perlèche The disease affects infants and sometimes adults particularly pellagrins and other debilitated individuals who cannot keep their mouths clean. Epidemics may occur the organism being transferred by carriers and by unclean utensils. The parasite is readily demonstrated among the epithelial cells scraped from a lesion.

In the newborn the condition appears to result from maternal monilial vulvovaginitis (Carter et al AmJObGyn 39 213 1940 Waters and Cartwright J 113 30 1939) Monilial vaginitis should be looked for during pregnancy and if present treated long before parturition.

Chronic deep infection of the oral mucosa is sometimes seen, producing leukoplakia and ulceration. Ephraim (BJD 61 414 1949) cured such a case with local agents and vitamin A Generous amounts of the B complex should be given, too

GLOSSITIS associated with monilia occurs in sprue pellagra and other avitaminoses. Hyperemia of the fungiform papillae and aphthous ulcers occur along with increased sensitiveness to hot fluids, spices and tobacco smoke In chronic cases there follows atrophy of the papillae so that the tongue is smooth and red, particularly along the sides. An important relationship cer

tainly exists between dietary deficiency and susceptibility to infection. The stomatitis of pellagra responds promptly and satisfactorily to treatment of the pellagra with the B complex. Monilial stomatitis is often seen following the disturbance of equilibrium of the flora when Aureomycin, Terramycin or other antibiotics have been given.

PERLÈCHE is an intertriginous inflammation of the labial commissures. A symptom, not a diagnosis, perlèche is sometimes due to monilia streptococci, contact irritants (toiletries, etc cf Stomatitis venenata) focal infection or avitaminosis and sometimes one fails to find the cause It is usually bilateral The mucosa is thickened and somewhat macerated The lesions extend a short distance onto the skin and onto the mucous membranes. In severe cases there are deep wrinkles and sore transverse fissures which cause considerable discomfort when the mouth is opened widely The lesions must be distinguished from the mucous patches and split papules of syphilis. When secondary syphilis affects the mouth there are always concomitant signs of widespread syphilitic disease Perleche seems to be transferable It has occurred in many individuals in one community such as an orphanage. Since Sebrell and Butler (PHRpts 53 2282 1938 54 2121 1939) showed that ariboflavinosis results in perlèche-like lesions, it is possible that the epidemics have been due rather to food deficiencies affecting a group of individuals than to transference of the disease by contagion. One may define perlèche as a symptom capable of being caused by parasites avitaminoses or contactant irritants. The monilial disease is treated locally by the use of mild astringent mouthwashes, which may advantageously contain myrrh or sodium perborate. In adults the dentures must be kept meticulously clean with nonirritating chemicals. The lesions themselves may be painted with 10% aqueous solution of silver nitrate and a layer of vaseline may be applied at night to protect the fissures from the moisture of drooling while asleep Silicote ointment serves well for this purpose (Reiches ADS 68 336 1953) Attention must be given to nutritional adequacy especially with respect to the B complex.

Monilial disease of mucous membranes in whatever form it appears may respond to the use of 2% aqueous solution of gentian violet a nontoxic but unsightly dye which sometimes irritates mucosae vigorously especially those of the female genitalia. While gentian violet is an effective antifungal agent, adequacy of nutrition in all its aspects must receive attention.

See Manson-Bah and Willoughby (QJM 23 411, 1930), glossitis in sprue, Miller (MJ Austral 2 649 1938) thrush Wright (BMJ 2 707 1940), perlèche in polyavitaminosis, Miller and Dark (AIntM 60 388, 1947) glossitis in sprue Ellenberg and Pollack (J 119 790, 1942) perlèche from malocclusion Nippert and McGilty (JaMAJ 32 298, 1943) perlèche from narrowed bite Finnerud (J 126 737 1944) perlèche Mann et al (JAmDentA 32 1357 1945) perlèche in edentulous mouth, Vamos (ActaD-V 19 241, 1949) perlèche and oral infection Vickers (BMJ 2 1091 1949), angular stomatitis from irritation by denture material, Greenfield (ADS 62 699 1950) perlèche following penicillin powder inhalations Edit (BMJ 2 1430 1950) thrush in infants

Monilial Vulvovaginitis and Pruritus Ani et Vulvae Vulvovaginitis and Infantile Dermatomycosis Vagina as Focus of Mycotic Infection.— Pruritus ani and pruritus vulvae are often due to Candida (or to other fungi such as Epidermophyton) and the infection is likely to be complicated by medicinal and traumatic irritation. Diabetes promotes pruritus because glucose encourages the growth of mycotic organisms. Monilial vaginitis is a common cause of pruritus even in women who do not have diabetes.

Monilial infestation of the vagina is commonplace and frequently asymptomatic It occurs in children virgins and senile women as well as parous ones. The disease may undergo spontaneous cure or it may become chronic with exacerbations at times over a period of months or years. Menstruation has the same temporary beneficial effect on the course of the infection as delivery does in cases associated with pregnancy Infantile oral thrush (q v) may result from infection in the birth canal (Hesseltine AmJObGyn 40 641 1940 Sage and Spaulding AmJDisChild 67 450 1944)

The following types of pudendal moniliasis are seen (Sutton J 110 1733, 1938)

1. Creamy vaginitis resembling oral thrush, with painful and reddened mucosa.
2. Creamy vulvitis, with considerable discharge but much redness or inflammation with or without a small amount of intertrigo which characteristically consists of small, grouped shallow vesicopustules.
3. Ulcerative vulvitis severe superficially ulcerated, with pain, lymphangitis and inguinal adenitis, possibly with mycotic infection of the bladder
4. Pseudoleukoplakic vulvitis in which the mucosa is whitish and opaque and the crusts are hard to remove, but no wrinkling papillomas or hyperkeratosis exists.
5. Eczematoid vulvitis, with a vesicopustular eruption consisting of small punctiform erosions, spreading and resembling intertrigo.
6. Mycotic pruritus of the vulva with few erosions, perhaps, and little discharge diagnosable only by smear and culture.
7. Vesiculopustular cutaneous form, manifesting disseminated involvement principally of external teguments with groups of small vesicopustules the vesicular stage being brief.
8. Cutaneous intertriginous eczematous form, which is intertrigo-like, with or without demonstrable organisms in the genitocrural plica, the inflammation spreading to the pubis, anal region and medial surfaces of the thighs, with but little visible involvement of the vulva.
9. Inconspicuous vaginitis with disseminated cutaneous involvement in the form of patches of intertriginous dermatitis with small vesicopustules not amenable to lasting therapeutic effects until the vaginal infestation has been treated properly
10. Moniliids, often consisting of pompholyx like patches of tiny deep-seated vesicles, which may absorb and result in superficial scaling or which may constitute an inflamed and oozing eczematous dermatitis and which depend primarily on the vulvovaginal focus.

Forms in the male are seen analogous to the types 4 5 6 7 and 8 (except the creamy discharge which is pus plus mucus from the cervical glands) involving the inguinal pudendal and perianal regions. They respond to similar treatment with 1 to 2% aqueous gentian violet and 1 5 000 potassium permanganate compresses, or to 2% sulfur in Vioform Cream Good ventilation, rest and exposure to daylight help Pruritus ani may in some instances be cured by Oidiomycin hyposensitization (Fowle et al JID 3 193 1940)

Diagnostic of monilial vulvovaginitis the exudate is acidic, and smears show budding parasites. Mycelium appears in the smears at times of maximum severity of clinical symptoms. After wiping an applicator over the mucosa one may stir it in 3 cc of isotonic saline solution then examine a drop of this on a slide Streak Sabouraud s medium to confirm

In treatment vaginal douches using 1 5 000 potassium permanganate and vaginal swabbing with 1 or 2% aqueous solution of gentian violet will control the condition Propionate compound jelly containing calcium and sodium propionates and propionic acid in a water-soluble vehicle has real utility as does AVC Cream

INFANTILE DERMATOMYCOSIS is usually monilial In the cases of infantile eczema so-called in which there occur deep red circular and oval circumscribed but coalescing patches of oozing itchy dermatitis the infection is likely to be monilial and it may have originated in the birth canal I have treated infantile mycotic dermatitis with great benefit by the widespread application of 2% aqueous solution of gentian violet for on the skin this drug is efficient nonirritating and nontoxic Asymptomatic monilial vaginitis in pregnant women—and it is far more common in pregnancy than at any other time—certainly ought to be treated before parturition

See LeHaye quoted by Popoff et al (AmJObGyn 18 318, 1929), clinical forms Plass et al (AmJObGyn 21 320, 1931) Hesseltine (J 100 1 7 1933) Bland et al (ADH 36 [illegible], 1937) experimental inoculation of pregnant and nonpregnant women, review, Hesseltine (AmJObGyn 34 855, 1937) iodine in treatment Woodruff and Hesseltine (AmJObGyn 36 467 1938) in pregnancy and newborn Hesseltine and Campbell (AmJObGyn 35 [illegible] 1938), strain of monilia in pregnant and in diabetic Jones and Martin (AmJObGyn 35 98 1938), [illegible] nonpregnant women Winston and Wickerham (YaleJBM 1 [illegible] 663, 1938), [illegible] flora Lyon and Cruickshank ([illegible] 4 [illegible] 194) in pregnancy Munich (CalMJ 39 [illegible], 1941) treatment with [illegible] sodium perborate [illegible] teaspoon to the quart for douches [illegible] SouthMJ 38 [illegible] 1944) [illegible] (ADH 55 113, 1947) undecylenic acid [illegible] ointment cream Council on Pharm (J [illegible] 1949) propionate compound jelly

MONILIASIS OF THE MALE GENITAL ORGANS —Penile infection as [illegible] vaginal are known and are often due to moniliasis of the wife Conjugal disease has been de-

scribed by Engman (ADS 1 370 1920) Dubreuilh and Joulia (AnndeD 3: 145, 1922) Odland and Hoffstadt (ADS 20: 335 1929) and others. These are curable by circumcision, cleanliness and treatment of the spouse unless they are maintained by urethritis or cystitis of mycotic origin, which probably occurs more often than it is diagnosed. Mycotic urethritis was described by Pi cane a d Coppolino (JTropM 41: 333, 1938) who referred to the description by Castellani (Lancet, 1920) of urethritis with white, red or black discharges due to f ngi Moniliasis of the urinary tract may result in blockage of the ureter by masses of mycelium, even fatal anuria (Taylor and Rundle: Lancet 1: 1-36, 1953)

Monilial Systemic and Generalized Cutaneous Infection.—Generalized cases are comparatively rare In these chronic infections the face ears, neck, upper chest and mouth are usually involved and thick, dry brownish crusts occur on the skin The majority of such cases, complicated by monilial pneumonitis and gastrointestinal infection eventuate fatally The lesions are dry with a tendency to crust and scale The patient complains of little itching except when the interdigital spaces are involved. At no time is severe inflammatory reaction present. The condition is afebrile Massive formation of mycelium and spores can be demonstrated in the lesions. Schultz (J 105 650 1935) is aptly quoted as to the formidable nature of the disorder when it becomes generalized and the remarkable ineffectiveness of any form of treatment Sulzberger (ADS 40 804 1939) claimed benefit in 1 patient with sulfapyridine Hazel and Lamb (OklaSMJ 27 395, 1934) reported a woman 23 years old who suffered from generalized moniliasis for 16 years, all treatment proving futile Antibiotic therapy made 3 of 4 patients worse as might be expected (Nikolowski and Miller DWchn 126 969 1952)

MONILIAL GRANULOMA.—Rare, remarkable granulomatous tumors have been described. Organisms are rife within the masses, which resemble those of bromoderma, according to Hauser and Rothman (ADS 61 297 1950) who reported a case and found 13 similar ones in the literature See Thomas (BJD 62 173 1950) Pluss and Kadas (JID 23 317 1954)

See Downing and Hazard (ADS 31 636, 1935) thick, dry brownish, crusted lesions in boy Carol et al. (AfDuS 175 177, 1938) young woman Danbolt (ActaD-V 21 28, 1940), old man with abscesses and bulla Tulipan and Kleinkatblit (ADS 46 642, 1942) case Strand and H bler (ADS 48 119 1943) case Strickler (AmJDisChild 68 382, 1944) child, helped with iodine ointment Ayres (ADS 53 377 1946) boy with nails, face, scalp lesions, also T purpureum

Visceral Moniliasis.—PULMONARY MONILIASIS, simulating tuberculosis, requires here only to be mentioned. Acute and chronic types hav been described (Warr: AnnIntM 5: 307 1931), with cough, mucopurulent sputum catarrh, fever dyspnea, anemia, sometimes fatality The wide variability of the clinical aspects was stressed by Baker et al. (J 102: 1203, 1934) Cavitation is rarely present. The disease often attacks asthmatics with bronchiectasis (Abrams KansMSJ 51: 562, 1950) Potassium iodide in doses of from 1 to 5 Gm. daily may help.

GASTROINTESTINAL MONILIASIS has received much study Presumably infection results from swallowing the organisms (Anderson: JInfectDis 21: 341 1917) Cultures of stools and of gastric contents were made in many diseases by Nye et al. (AmJMedSci 178: 153, 1939) who found C albicans present in higher incidence in pernicious anemia and achylia, yet believed the fungus not important in the etiology of sprue or avitaminosis. Monilial gastritis has been described as having the potentiality for ulceration or even perforation (Bearse AmJDigestDis 5 674 1938) The organisms are present in the gut in generalized cases, and no way for certainly eliminating them is presently known (see Treatment) The administration of antibacterial antibiotics allows monilia to luxuriate in the gut (see Antibiotics and Moniliasis, p. 549) Compare Acrodermatitis enteropathica (p 644)

MONILIAL ENDOCARDITIS was recognized from blood cultures in several cases by Pasternack (AmJClinPath 12 496 1942) Kunstadter et al. (J 149: 829 1952) found 24 cases of mycotic endocarditis in the literature of which 9 were known to have been monilial, and 5 of these occurred in drug addicts. Their patient was an infant, a unique case

MONILIAL MENINGITIS has been known to occur though it is rare Pressure of the spinal fluid is high, giving rise to headache and edema of the optic nerve head. Diagnosis depends on demonstration of the organism in the spinal fluid. The patient of Zimmerman et al. (J 135: 145 1947) who also had oral thrush, recovered probably as the result of the administration of streptomycin. The disease was fatal in the case reported by Halpert and Wilkins (J 130 932, 1946)

SEPTICEMIA was present in the pulmonic and disseminated case of French and Sheard (CanadMAJ 71 238 1954) *Candida albicans* was present in the neutrophil leukocytes. Miliary granulomatous and necrotic lesions were found at autopsy



Fig. 715.—Monilial dermatitis of feet. (Dr. Royal S. Montgomery.)





Figs. 716 and 717.—Monilial granuloma, [illegible] case of Drs. Stephan Rothman and F. V. Hauser (AD&S 61: 297, 1950.)

Immunology Skin Tests and Vaccinal Therapy in Moniliasis.—The humoral and tissue reactions to Oidiomycin are analogous with those to trichophytin. Monilia are potent sensitizers. Treatment by vaccinal hyposensitization has basis in theory but in practice attacks upon the foci of the organisms by means of antiseptics and débridement afford better effect. Trichophyton and Candida are immunologically distinct Skin tests with monilial extracts may be interpreted much as trichophytin tests are (Lewis et al NYSJM 37: 878 1937 38 859 1938) They are of little practical value Patients, for example with monilial pruritus ani, hyposensitized by allergists with Oidiomycin, come to me to be cured by other means.

MONILIDS.—These allergic eruptions occurring specifically in moniliasis are the counterparts of trichophytids. As a rule they consist of tiny closely aggregated, intraepidermal vesicles, and they may be set upon a more or less inflamed base located on the hands, legs or flexures. They may depend on foci in the nails, glabrous skin, tonsils, mouth, vagina, auditory canal or gastrointestinal tract It is commonplace to cure pompholyx of the hands by treating tinea of the feet when pompholyx is a trichophytid I have cured repetitious, pompholyx like eruptions of the hands by means of douches of 1:3 000 potassium permanganate and the application of gentian violet to the genitalia, without treating the hands themselves.

See Hopkins (ADS 25 593 1932) sensitization from gastrointestinal focus; Biberstein and Epstein (ArDuS 165 716, 1932) clinical picture and immunity; Sulzberger (JImmunol 23: 73 1932), immunologic differences between trichophytin and Oidiomycin, preparation of fungus extracts Kerr et al. (JAllergy 5 288, 1934) monilial sensitivity separate from that of trichophyton and epidermophyton.

Etiology—Infection with monilia like all infections, depends upon both the soil and the organism. In food deficiencies, particularly avitaminosis B and in diabetes the individual is more vulnerable Environmental circumstances may favor or inhibit the growth of the organisms, and moisture, warmth and darkness, as in tinea abet pathogenicity *C albicans* is described on p 478

ANTIBIOTICS AND MONILIASIS.—Moniliasis is a recognized complication of antibiotic therapy (*Edit: SouthMJ 44: 231, 1951*) *Stomatitis following therapy for brucellosis* was reported by Harris (J 14 161 1950) and black hairy tongue consequent upon antibiotics was reported by Downing (NEngJM 4 1013 1950) The stools, when bacterial growth is suppressed, become curiously foul, or perhaps odorless, and diarrheic; and pilar or perianal dermatitis, when it appears, shows an abundance of Candida. Many cases of clinical moniliasis following the use of penicillin, Aureomycin and chloramphenicol were reported by Woods et al. (J 145 207 1950) See also Reiches (ADS 64 604 1951); Seligmann (PSExpB 79: 481 1952); Edit (J 149 762, 1952) Candida was found in the peritoneum of a patient of Reynell et al. (BMJ 1: 919 1953) who died following perforation of a peptic ulcer after he had received Aureomycin and ACTH. In an excellent review of the subject Hutchison (JKansMS 54 436 1953) collated 2 fatalities, including 15 from endocarditis and 6 from meningitis. Anorectal complications of antibiotic therapy in 300 patients were reviewed by Manheim and Alexander (NYSJM 54 231 1954) whose cases included pruritus in 207 multiple fissures in 51 ulcerative proctitis in 14 abscesses, fistulae or ulcers necessitating surgery in 14 and ulcerative colitis in 5 Yet most cases in fact recover spontaneously and local therapy is quite effective (Turell and Maynard: J 156 17 1954) Permanganate soak and 2% sulfur in Vioform Cream are useful. Interpreting the perianal dermatitis as representative of pellagra, Morris (GP 9 71 1954) eel traced the value of nicotinic acid. Monilia must be present already if they are to luxuriate under antibiotic therapy *which cannot create the infection according to Robinson (ADS 70: 640 1954)*; in the discussion of this paper hazards of antibiotics in older people who are more likely than young persons to harbor the organisms in the gut, was stressed by Swartz. I have seen significant trouble only in individuals grossly overdosed, whose complication would have been trivial if it had been recognized early and the drug discontinued. Robinson set the figure at 16% as the incidence of *C. albicans* occurring among the normal flora of the gut. He gave about the same figure for its presence in the vaginal tract of normal pregnant women and the oropharynx of normal persons. The growth of *C albicans* on artificial media is neither stimulated or depressed by antibacterial antibiotics he stated, so that the development of monilia is following antibiotic therapy may result from lowered resistance to the fungus perhaps because it overgrows when competing organisms are suppressed. Yet only has vulvovaginal moniliasis increased in incidence since the introduction of broad spectrum antibiotics, but also moniliasis of the male genitalia, evidently as a result of sexual communication of the infection, believed Walsman (ADS 70: 718, 1954)

Cortisone and ACTH therapy was accredited with increasing susceptibility to monilia by Brathund and Holten (abs J 156: 1119 1954) I have not observed this.

Treatment.—To be comprehensive and permanently effective treatment must be directed at the eradication of all *foci* both in the skin and elsewhere. The accessible parasitized tissues should be kept dry and ointments have little to commend them if they allow a film of sweat or ooze to collect, protected from evaporation. Gentian violet has been used for many years and it is one of the most effective parasiticides. Baths in 1 8 000 bichloride of mercury are useful. Douches of 1 5 000 potassium permanganate are fairly satisfactory bichloride of mercury must not be used for this purpose. In pregnancy suppositories of 1 1 000 Merthiolate are of sufficient value to warrant their trial (McIlrath MJAustral 2 54, 1946) Cool, moist packs for 15 to 30 minutes, alternated with drying in a current of air under the influence of radiant heat are effective Roentgen therapy offers temporary alleviation of inflammation, but it must not be repeated beyond the limit of tolerance and of itself it is not curative.

In paronychia, 5% chrysarobin in chloroform is a useful paint.

In onychomycosis, débridement 10% $AgNO_3$ and x ray therapy may be used.

In stomatitis, cleanliness is an important prophylactic measure. Fingers should not be put into babies mouths. Gentian violet has an important place Sodium perborate may be used both for tooth powder and for mouthwash. Vitamin B complex should be given in adequate dosage (Bechet NYSJM 43: 2065 1943)

The generalized cases tax every medical resource and almost all cases on record have turned out badly Hope may be afforded by Mycostatin an antifungal antibiotic. Mycostatin (Nystatin, Squibb) was said to have helped *several cases, according to communications received by Squibb from Holt,* Robinson, and Kunstadter Their literature states that Mycostatin is derived from cultures of *Streptomyces noursei* (Hazen and Brown Sci 112 423 1950) Pale yellow almost colorless, in crystalline form, it is less soluble than when only partially purified is relatively stable when dry but breaks down rapidly in the presence of water It inhibits or kills many fungi but not actinomycetes (Tarbet et al Mycologia 45 627 1953 Raubitschek et al Antibiot&Chemother 2 179 1952) being most effective against yeastlike fungi in their growing stage and less active against spores. Given orally it is poorly absorbed and virtually nontoxic. Large doses have caused nausea and vomiting side effects have been absent or trivial. The drug may be prescribed for the suppression of intestinal fungi, and when given concurrently with tetracycline it apparently protects against the overgrowth of monilia. An old woman with systemic cutaneous and urinary tract infection was reported cured with Mycostatin by Robinson (*JID* 24 375 1955) who prescribed tablets of 500,000 units t i d and an ointment containing the substance for use in the vagina The ointment is effectual but Nystatin irritates some individuals even in a concentration of only 100 000 units per gram Osbourn (AD 72 371 1955) recommended a shake lotion containing 3 tablets in 60 cc of vehicle.

See Widt (ADS 18 479 1928) yeastlike organisms cultivated from 152 of 721 patients with scaling or crusting lesions, some resembling seborrheic dermatitis Stovall and Bubolz (JInfectDis 50 73, 1932 AmJPubH 22 493, 1932 JLCM 18 898, 1933) cultural features, pathogenicity Denham and Hopkins (ADS 28 532, 1933) normal flora does not contain *C albicans* Cornbleet (J 104 1976, 1935) higher concentration of reducing substances in sweat of infected persons than of normal Lamb and Lamb (JInfectDis 56 8, 1935) fermentation and precipitation distinctions, Smith and Lewis (SouthMJ 29 1087 1936) M causing ulcers of ankle responsive to KI Martin et al (JBact 34 99 1937), classification and culture technic Anderson (MJAustral 2 57 1946) cultivation on corn meal extract with ... George and Plunkett (JID 10 337 1948) dissociation of *C albicans* in cultures Riley and Flower (JID 18 285, 1950) inhibition by gentian violet greatly exceeds that by Castellani paint, of which basic fuchsin is the effective ingredient in vitro

TORULOSIS (CRYPTOCOCCOSIS EUROPEAN BLASTOMYCOSIS)

Torulae are yeastlike plants distinguished from higher yeasts in that they form neither endospores nor myceliums, and from Saccharomyces in that

torulae are pathogenic and characteristically do not ferment sugars (Mitchell J 106 450 1936) Rarely *Cryptococcus neoformans* (*Torula histolytica*) produces superficial lesions, but it does not ordinarily invade the skin.

Cutaneous lesions have not been uniform in their clinical manifestations. There have been described (Wile ADS 31 58 1935) acneiform involvement of the forehead furunculoid sores of the thighs associated with broad patches



Fig. 718.—Torulosis. (Dr Udo J Wile.)
Fig. 719.—Torulosis affecting gingivae (Urbach AfDuS 162 401, 1930.)
Fig. 720.—Torula grown from case of Dr Udo Wile.
Fig. 721.—Torula in tissues from case of Dr Udo Wile.

of induration of thigh and popliteal tissues, gummas of the abdomen with hard purplish nodules of the cheeks, swellings on the forehead and neck and over the tibia a granuloma confined to the foot and a mycetoma-like lesion of the foot. Diagnosis depends on identification of the causative fungus. Torulae cause fatal tuberculoid meningitis or encephalitis. They are as often associated with Hodgkin s disease as tuberculosis is (Mallory NEngJM 210 1291 1934)

In their review Cawley et al. (JID 14: 327, 1950) described 13 cases of cutaneous torulosis, 10 of which were associated with central nervous system involvement. The skin lesions in 6 cases were located on the face, scalp and neck; in they were on the trunk. Four were acneiform, 4 pustular or nodular, 3 ulcerative abscesses, and granuloma. 1 showed nodules and plaques resembling ecchymoses and 1 a sinus tract. Mucosal lesions were present in 4 cases, showing violaceous nodules of granulation tissue, tumors and ulcerations. Mucosal lesions occurred on the gums, palate, pharynx, tonsillar pillars, buccal mucosa, nasopharynx and nasal septum. The only lesions clinically diagnostic were the acneiform ones. These authors found 120 human cases in the literature and added their 5 cases to the total.



Fig. 721.—Rhinosporidiosis: mucosal fungations and cutaneous implants in an Indian. (Drs. F. Allen and M. L. Da[illegible] IndMedGaz 77: 376, 1936.)

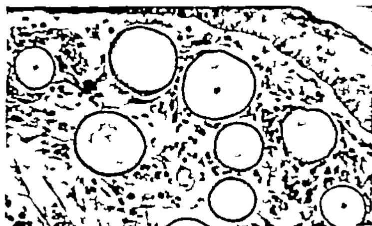


Fig. 722.—Rhinosporidiosis: section showing cystic pattern. (Dr. Ed[illegible] A. Gall.)

Treatment is unsatisfactory, although roentgen therapy, iodides and gentian violet may be tried and excision may be performed if feasible. One may hope that stilbamidine or related compounds (see Blastomycosis, treatment) will prove effectual.

See Stoddard and Cutler (Torula Infections in Man, Rockefeller Inst. N. Y., 1916); Urbach and Zach (ArDerm 162: 401, 1930), oral primary; Weidman (SouthMJ 6: 85, 1933), case in monkey; Benham (ADS 30: 385, 1934; JInfectDis 57: 255, 1935), mycology; Fitchett and Weidman (ArchPath 18: 225, 1934), associated with Hodgkin; Mook and Moore (ADS 33: 951, 1936), fatal, brain and skin; Levin (ArIntM 59: 667, 1937), central nervous; [illegible] (ADS 37: 461, 1938), deep cutaneous lesions; [illegible] Tolhurst (Human Torulosis, [illegible] Univ. Press, 1936), monograph, 12 cases; Daniel et al. (Lancet 1: 53, 1949), central nervous; [illegible] (JID 12: 271, 1949), cryptococcal [illegible] Rosa, pathogenicity; Kligman and Weidman (ADS 60: [illegible] 1949), no [illegible] tested helped mice infected intraperitoneally; Fisher (JhuJHH 86: 383, 1950), 3 cases; Gandy (ADS 62: 97, 195), primary ulcer on nose; Cook (J 146: 1103, 1951), meningitis; Baker (J 150: 1577, 1952), resectable pulmonary lesion; Linell et al. (ActaD-V 33: 10., 1953), acneiform exacerbation in chronic pulmonary case.

RHINOSPORIDIOSIS

Rhinosporidium seeberi is a phycomycetic parasite occurring in the form of spherules of various dimensions within the polypoid masses which its presence elicits. Young cysts some 6 μ in diameter have a chitinoid envelope, a vacuolar cytoplasm and vesicular nucleus. Old cysts reach a diameter of 300 μ and have a cellulose-like envelope enclosing numerous singly nucleated spores within a mucinous brown ground substance. The organism has never been cultivated.

Primarily affecting the mucous membranes, usually of the nose and sometimes of the conjunctivae, the lesions due to *R. seeberi* are pedunculated or sessile strawberry-like or raspberry-like tumors consisting of tightly packed tendrils suggestive of filiform verrucae. Cutaneous lesions, solitary or multiple, are usually the result of inoculation from foci located elsewhere according to Allen and Dave (IndMGaz 71: 376, 1936) who described 60 cases and gave a full bibliography. Ocular cases were collated by Kaye (BJOphth 22: 449, 1938); he likened the typical lesion to a cockscomb and described the villous polypi with easily bleeding granulations, the crypts of thickened epithelium, the granulomatous inflammation with plasma cells and lymphocytes, and the rhinosporidium cysts, chiefly subepithelial, their white sporangia macroscopically visible on the surface of the lesion. The infection remains local but is unsightly, uncomfortable and sometimes obstructive to air passages. Most cases have occurred in India and South Africa, but of the 12 reported by 194– in the United States, 4 were Texan (Pasternack: TexasSJM 38: 285, 194–). Cure may be sought with surgical excision or cauterization. Neostibosan seemed adjunctively helpful to Allen and Dave.

See Ashworth (TransRoySocEdi 53: 301, 1923) bibliography; Karunaratne (JPathBact 42: 193, 1936) bibliography after Ashworth's, color plates; Caldwell and Roberts (J 110: 1641, 1938) seventh U. S. A. case, all nasal; Ruchman (AOtol 30: 239, 1939) nasal case helped by antimony, as suggested by Wright (IndMJ 57: 8: 81, 1922); Ormsby and Brown (ADS 54: 231, 1946) conjunctival case.

THE MYCETOMAS

Mycetomas are granulomatous mycotic lesions enclosing fungus grains of various shapes. The grains are formed by felted mycelium and they are discharged through more or less extensive fistulas. In contrast with the tineas, which in general produce only superficial disease, the mycetomas are due to other fungi which produce deeply seated granulomatous inflammation. They gain access into the human body through injuries as a rule, and the foot is particularly vulnerable.

Madura Foot.—This is a clinical entity capable of being caused by various organisms. A typical mycetoma, it is characterized by swelling and gradual disintegration of the subcutaneous structures and the formation of sinuses which open onto the surface of the skin. These mycetomas are characterized by grains formed by voluminous, septate mycelial filaments possessing definite cross walls and forming chlamydospores.

Following an injury, an incised or puncture wound, there develop within a few weeks swelling, edema and indurated nodules. More nodes develop until the affected patch presents a purplish, knobby appearance as in actinomycosis. Some nodules remain firm and solid, but the majority of them undergo necrosis, so as to become perforated by slender, tortuous channels which extend deeply and let escape variable amounts of seropurulent fluid containing variously colored grains. Spontaneous cure is extremely rare. The course may run for many years. Metastasis ordinarily does not occur, but the progress locally is such as to eventuate almost inevitably in amputation.

The disease is seen in tropical climates, where numerous individuals go barefoot, but an occasional case occurs in North America. Barns et al. (AmJClinPath 15: 35, 1945) summarized the 35 cases recorded as occurring in the U. S. A. and Canada by 1945. See Edit (J 141: 1800, 1949) giving description and review as follows: many species of fungi belonging to several genera have been implicated in the various types of maduromycosis, which, nevertheless, may clinically resemble each other closely. Cases may be divided into three groups: (1) those with changes confined to superficial structures in the form of granulomatous lesions of the skin or of the skin and subcutaneous tissues; (2) those with 1 or more fibrous, fatty or occasionally cystic nodules without ulceration of the overlying skin; and (3) the commonest group, wherein lesions are present as multiple subcutaneous nodules which are movable, painless and nontender. Spontaneously or sometimes as a result of injury the nodules rupture and discharge mucopurulent material containing white, yellow or black granules, depending on the particular parasite present, the white or yellow varieties predominating. Maduromycoses have been classed according to the blackish, whitish or reddish color of the fungus grains, but



Fig. 724.—Mycetoma. (Sutton J 60: 1330 1912.)



Fig. 725.—Madura foot, Texas case. (Dr O. Garcia.)



Fig. 726.—Mycetoma.



Fig. 727.—Section of foot amputated because of maduromycosis.

grains of the same color may be produced by more than one parasite. There have been identified as causative organisms species of Nocardia, Allescheria, Aspergillus, Penicillium, Madurella, Indiella, Cephalosporium, Monosporium, and Glenospora (Conant et al.: Manual of Clinical Mycology Saunders, 1945 modifying Gammel: ADS 15: 41 1927)

TREATMENT.—Potassium iodide copper sulfate and various internal remedies, including sulfonamides (Dixon ValMonth 68 281 1941) and penicillin, may be tried. One of 2 patients of Twining et al. (USNMB 46 417 1946) was cured by penicillin the other relapsed and required amputation. Temporary improvement may follow roentgen therapy. Secondary infection may cause death. Treatment is likely to entail eventual amputation.

MADUROMYCOSIS. ETIOLOGIC CLASSIFICATION ACCORDING TO BRUMPT
(Précis de Parasitologie Masson, 1949)

Black Grain Type

ALEUROSPORIA
- *Glenospora semoi* (Chalmers and Archibald, 1917) India.
- *G. khartoumensis* (Chalmers and Archibald, 1916) Africa.
- *G. clapieri* (Catanei, 1917) Africa.
- *G. gammeli* (Pollacci and Nannizzi, 192?) North America.
- *Scedosporium sclerotiale* (Pepere 1914) Europe

PHIALIDES
- *Aspergillus bouffardi* (Brumpt, 1905) Somaliland.
- *? A. mycetomi* (Gelonesi, 1927) Somaliland.
- *A. nidulans* var. *nicollei* (Pinoy, 1911) Tunis.
- *A. kecallieri* (Mangin, 1909)
- *? Penicillium mycetomagenum* (Mantelli and Negri, 1915) Europe.

TORULAE
- *T. jeanselmei* (Langeron, 1928) Antilles.

PHYCOMYCETES
- *Mucor (?) mycetomi* (Gelonesi, 1927) Somaliland.

HYPHOMYCETES
- *Madurella americana* (Gammel, Miskdjian and Thatcher 19?6) Texas.
- *M. keroi* (Brumpt, 1910) Italy
- *M. ikedai* (Gammel, 19?7) North America.
- *M. mycetomi* (Laveran, 1902) cosmopolite
- *M. oswaldoi* (Horta, 1919) Brazil.
- *M. ramiroi* (P. da Silva, 1919) Brazil.
- *M. rifana* (Gastaminza, 1929) Morocco
- *M. t barkae* (Blanc and Brun, 1919) Tunis.
- *M. tozeuri* (Nicolle and Pinoy 1908) Tunis.

White or Yellowish White Grain Type

ALEUROSPORIA
- *Scedosporium apiospermum* (Saccardo 1911) cosmopolite.
- *Indiella mansoni* (Brumpt, 1906) Asia.
- *I. reynieri* (Brumpt, 1906), Paris, Greece
- *I. brumpti* (P. Piraja, 1922) Brazil.

SPOROPHOREA
- *Cephalosporium recifei* (Leao and Lobo, 19?4), Brazil.
- *Cephalosporium granulomatis* (Weidman and Kligman 1945)
- *Acremonium potroni* (Vuillemin, 1911) Algeria.
- *Acremoniella lutzi* (Area Leao and Lobo, 1930)

PLECTASCALES
- *Sterigmatocystis nidulans* (Eidam, 1883) Tunis and Algeria.
- *Allescheria boydii* (Shear 1921) U. S. A.

Greenish Yellow Grain Type

- *Aspergillus amstelodami* (Mangin, 1900) Brazil.

Red Grain Type

- *Aspe gillus* (case of Balfour and Archibald) Africa.
- *Rubromadurella langeroni* (Talice 1935) Uruguay

See Castellani and Chalmers (Tropical Diseases, 1920 p. 2110); Gelman and Gammel (Abury 31: 298, 1932), white grain case, *Monosporium apiospermum*; Shaw and Macgregor (CanadMAJ 33 23, 1935), first Canadian case *M. apiospermum*; Dowding (CanadMAJ 33 28, 1935); Aldridge and Kirk (BJOphth 24 211 1940) yellow; Fienberg (AmJClinPath 14 230 1944) case, *M. apiospermum*; Twining (ADS 50 332, 1944) case, *M. apiospermum*; Symmers (APath 39: 358, 1945) rabbit inoculations with *Phialophora jeanselmei*; Calero (ADS 55 761, 1947) Panama cases; Elliott (J 142 882, 1950); Quinland and Chenault (SouthMJ 43 661 1950) case, *M. apiospermum* contracted in Europe; Carrión (Mycologia 43 522, 1951) case, *Cephalosporium falciforme*

Actinomycosis (Lumpy Jaw) is produced by various microaerophilic fungi which within the tissues form grains composed of fine nonseptate mycelial filaments, in which the partitions are invisible or difficult to demonstrate and in which chlamydospores are not formed. *Actinomyces bovis* is the commonest cause in the United States. It provokes sluggish, nodular infiltrated lesions.







Fig. 728.—Actinomycosis. (Dr Jabez N J ckson.)
Fig 729.—Actinomycosis. (Dr T W Allsworthy.)
Fig. 730.—Actinomycosi of the neck and jaw showing granulomas and sinu tracts draining through the skin. (Dr H. O. Varney.)



Fig. 731.—Actinomycosis. (Dr Sam J Sweitzer.)

which tend to undergo central necrosis and to form chronic subcutaneous abscesses and sinus tracts. The lesions develop slowly Inoculation through the teeth gums or tonsils results in the development of infiltration in the jaw (lumpy jaw) and neck. The nodules may require weeks or months to soften and to become fluctuant Overlying tissue slough, and purulent matter





Fig. 732.—Actinomyces Gram stain showing mycelium of the interior of the fungus mass. (Dr Frederick Wakeman.)

Fig. 733.—Actinomyces ray fungus seen in section Gram stain, showing filaments in interior "Clubs" are seen at the upper margin of the grain. (Dr Frederick Wakeman.)



Fig. 734.—Actinomycetic granule in pus, unstained, X75. (Dr E. Muskatblit.)

mixed with small masses of fungus resembling grains of sulfur discharge from them. The involved region is usually isolated, but generalization may occur The usually yellowish gray granular masses of fungi in the discharge should serve to differentiate actinomycosis from syphilis, tuberculosis, sarcoma or carcinoma. Pus is put in a tube of water and shaken the sulfur granules sink (Colebrook Lancet 1 893 1921)

The organism may be carried nonpathogenic, for it has been found in pus from tonsils and from pyorrhea in, respectively 11 and 18 of 100 examinations performed by Slack (JBact 43 193 1942) Oral trauma appears to be causally related to invasion by Actinomyces (Sullivan and Goldsworthy JPathBact 51 253 1940) *A. israeli* is said to be a normal member of the oral flora (Robinson and Ennever OralSurg 1 850 1948) Aspiration probably accounts for primary pulmonic cases. The disease has followed human bites (Robinson J 124 1049 1944)

Cervicofacial cases are the commonest Pulmonary and deep abdominal cases follow in order of frequency and any part of the body may be infected. In the tongue primary actinomycosis has its onset as a painful swelling which is round, tender and located in the anterior third it becomes softer discolored, purplish and painful, and matter discharges through sinuses (Cameron J 99 1146 1932)

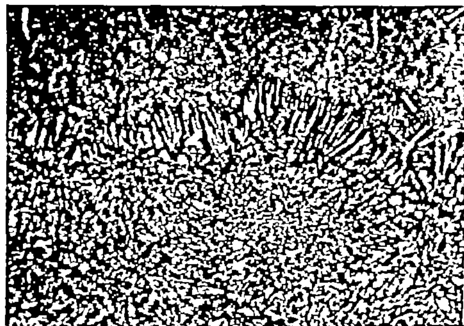


Fig. 31.—Actinomycetic granule in pus X60 (Dr E. Muskatblit.)

Cases primary in the skin, with subsequent fatal hepatic involvement in 1 were reported by Salzmann and Kessler (ADS 36 131 1937) The skin primary which resembled a felon resulted in fatal chronic purulent meningitis reported Morrison et al. (J 110 1552 1938) Infection in the ear not rarely leads to meningitis 76 such cases were collated by Cann and Hollis Lancet 1 130 1931 When the nervous system is involved, the spinal fluid usually is thickly purulent with a high count of polymorphonuclear leukocytes and the patient, appearing not markedly toxic, carries a fever of only 101 F or so and shows paralyses of several cranial nerves Friedman and Levy InternatClin 2 36, 1931 Such a patient may die suddenly

Etiology —Actinomyces may live as saprophytes on some kinds of vegetation and even on human tissues and in tonsillar crypts Their introduction as parasites is usually due to an injury which of itself may be of seeming inconsequence According to Brumpt (1949) the Hyphomycetes are fungi which have a white or dust filamented thallus and which reproduce exclusively by conidia Hyphomycetes with fine nonseptate mycelial filaments 1 μ or smaller in diameter branching laterally having homogeneous content and lacking distinct nuclei, often dissociating into bacteroid particles are Microsiphonales All of the Microsiphonales parasitic on man may be classed in the genera Actinomyces and Nocardia.

Pathology —Actinomycetic parasites develop well in all tissues of the body but clinically they seem to spare the lymph nodes In sections of the granulomas macrophages filled with mycelial filaments are numerous near the vessels Masses of fungi are scattered within the granulation tissue forming the well known clubs The detailed structure of the clubs differs in different kinds of actinomycetic infection and may serve the expert for differentiation, although cultural studies are necessary for exact identification. Problems in diagnosis were elucidated by Weed and Baggenstoss (AmJClinPath 19 201 1949) who observed, in studying

35 fatal cases that one may find structures resembling sulfur granules not yet containing Actinomyces while some cases yield the anaerobic organism on culture but never exhibit sulfur granules.

PROGNOSIS.—Most of the localized cases undergo recovery. Many systemic cases have died. Systemic involvement following upon localized disease is always possible. The disease may heal spontaneously but this is very exceptional. Its progress causes cachexia, suppuration, reduced resistance, and secondary infection. Sulfonamide and antibiotic therapy has in recent years improved the outlook greatly.

ACTINOMYCOSES. ETIOLOGIC CLASSIFICATION ACCORDING TO BRUMPT (1949)

Black Grain Type

Case of Babes (1898) Roumania.
Case of Mironescu (1910), Roumania.
Case of F. de Almeida (1930), hepatic Brazil.
Case of Beron (1931) Bulgaria.
Actinomyces paraguayensis (de Almeida 1940)

Yellow Grain Type

With clubs

BREVIORES (ACTINOMYCES):
- *Actinomyces israeli* (Kruse 1896) cosmopolit [Affects bones anaerobic.]
- *A. thibiergei* (Ravaut and Pinoy 1906) [Does not affect bones.]

MINORES (NOCARDIA):
- *N. mexicanus* (Boyd and Crutchfield, 1921) Mexico and Texas.
- *N. transvalensis*, *N. pretoriana* (Pijper and Pullinger 1927) South Africa.

Without clubs

MAJORES (STREPTOMYCES):
- *S. liquefaciens* (Hesse 1892) Europe
- *S. gartoni* (Brumpt, 1910) Europe

MINORES (NOCARDIA):
- *N. asteroides* (Eppinger 1890) cosmopolite
- *N. brasiliensis* (Lindenberg, 1909) Brazil.
- *N. brumpti* (Bordjoski and Milochevitch, 1915) Jugoslavia.
- *N. madurae* (Vincent 1894) cosmopolite
- *N. nicollei* (Delanoë, 1928) North Africa.
- *N. convoluta* (Chalmers and Christopherson, 1916) Sudan.

INCERTAE SEDIS:
- *A. krausei* (Chester 1901) Europe
- *A. ponceti* (Verdun, 1912) Europe
- *A. gerrai* (Lageron 1930) San Salvador [Affects bones.]

Red or Reddish Grains

Without clubs

MINORES (NOCARDIA):
- *N. somaliensis* (Brumpt, 1906) Africa. [Affects bones.]
- *N. bahiensis* (P. da Silva, 1919) Brazil.
- *N. mycetomae argentinae* (Greco, 1901 Durante, 1911) Argentina.
- *N. pelletieri* (Laveran, 1906), Africa.
- *N. africana* (Pijper and Pullinger 1927) [Affects bones.]
- *N. genesii* (Froes, 1930) Brazil.

TREATMENT.—Iodides have long been standard therapy but sulfonamides and penicillin soon proved their worth as they became available. The patient of McCrea et al. (JLCM 30 509 1945) responded to 120 000 units of penicillin q. 3 h. after failing to respond to 20 000. Of 11 cervicofacial cases 7 were cured and 4 arrested by Dobson and Cutting (J 116 272, 1941; 128 856 1945) using penicillin or a sulfonamide one being sometimes more effective than the other. In a study of 16 cervicofacial cases, Lamb et al. (J 134: 351, 1947) concluded that roentgen therapy and sulfadiazine by mouth suffice in uncomplicated instances, while penicillin must sometimes be given in large doses over a long period of time and is valuable. Penicillin in 45 cases gave best result in pulmonary abdominal and pelvic infections, reported Nichols and Herrell (JLCM 32 1405 1947). A sulfonamide and penicillin cured the patient with central nervous involvement of Jacobson and Cloward (J 137 769 1948). The patient of Arnold and Austin (J 138 955 1948) with lumpy jaw not helped much by penicillin, was cured by Diasone 1 Gm. daily. Of the 6 patients of Chanton et al (SouthMJ 41 1022, 1948) only 2 required surgery when treated with both penicillin and a sulfonamide along with transfusions. Extremely large doses of penicillin may succeed when modest doses have not produced benefit (Sanford and Barnes Surg 711 1949).

Aureomycin cured a mandibular infection that followed extraction of a tooth (McVay et al. J 143 1067 1950 AnnIntM 38 955 1953) and a cervical case of Wright and Lowen (J 144 21, 1950) Terramycin likewise was effectual in doses of from 750 to 2,000 mg daily in 7 cases of cervicofacial infection with *A bovis* (Lane et al. J 151 986 1953) Thymol 10 to 20% in olive oil, has been applied locally and injected into the sinuses, and 1 to 2 Gm of thymol in capsules was given by mouth daily on an empty stomach (Myers J 108 1875 1937 Joyce AnnSurg 108 910 1938 Glemens JPed 16 487 1940) Isoniazid is inhibitory in vitro and, given to 3 patients, yielded results thought encouraging by McVay and Sprunt (J 153 95 1953)

Locally surgical measures are important for incision and drainage débridement and sometimes, plastic repair work contribute to the cure. Osteomyelitis of the jaw is not uncommon and requires the help of the oral or orthopedic surgeon.





Fig 34—Facial mycetoma due to *Nocardia mexicana* (Gradwohl, et al. Clinical Tropical Medicine Mosby 1951)

Fig 35—Nocardiosis of forearm, 5 months duration. (Dr Sam E. Sweitzer)

Roentgen therapy was of greater repute before the modern drugs became available than it is now yet it will, properly used resolve to a significant degree the chronic granulomatous tissue It was at one time adjudged the most important measure available in addition to surgical drainage and the *administration of iodides* (Keijser Strahlenther 56 449 1936)

See Thomassen (L Echo Vet 1885) introduction of iodide in treating tongue cases in cattle popularized by Nocard in 1892 Wolff and Israel (ArPathAnat 126 11 1891) original description of organism most commonly causati of actinomycosis Jacobson (MedJ&Rec 132 342, 3 9 431 1930 5 cases and review Lord and Trevett (JInfectDis 58 115, 1936) organisms in normal mouth Neuber (WienKlinWschr 50 11 6, 193) attempted immunologic treatment Hay and Tribedi BJS rg 26 30, 1938 mammary cases, Cope (Actinomycosis Oxford Univ Press, 1938 p 245) monograph, color plates, quotes Wright who has established cases in 1903 Walker (Lancet 1 1219, 1938), bilomical case following sulfanilamide, cured with sulfanilamide Miller and Fell (J 112 31 1939) case confirming Walker Hall (J 112 219 1939) salpinx ... red with sulfanilamide Tribedi and Mukherjee (IJSurg 2 36, 1939) 35 Calcutta Medical College cases Kolshalk and Wilen (WestJSurg 48 212, 1940), 11 cases due to *A bovis* Franklin (AnnIntM 13 1293 1940 *A muris* Davis (ArchSurg 52 447 1941 46 cases, ... of Michigan, grass-chewing and proximity to animals not the significant in etiology Dobby and Knighton JInfectDis 69 146 1941), oral flora Hamilton and Kirkpatrick BMJ 2 ... 9 194) penicillin cures MacGregor (ProcRoySocM 38 619 1945) differences between human and bovine strains, ... relations to penicillin sensitivity Meckstroth (ADS 66 ... 96 194 penicillin cure review Farris and Douglas (Surg 24 414, 1947), penicillin and sulf both ... cure 5 cases, bilomical, Robinson and Taker (AnnRheum Dis 2 1, 1949) 4 Southern California cases sulf and penicillin not so wonderful Waksman (The Actinomycetes Herbert Hafner N Y 1950), mycology follow Bergey classification Garrod (BMJ 1 1 63, 1952) antibiotic sensitivity in 12 strains of *A israeli* penicillin best

Oosporosea.—Oospora was the genus name now obsolete, but once used to apply to the organisms seen in diseases resembling actinomycosis but in which actinomycotic grains were absent (Brumpt)

Nocardiosis.—Nocardia comprise, according to Brumpt (Précis de Parasitologie Masson, 1949 p. 1 13) a genus of Actinomycetaceae of the following features: easy to cultivate; powdery odorless colonies on solid media resembling those of *Myco tuberculosis* filaments rarely branching almost always acid fast; not liquefying gelatin or producing diastase.

Numerous species are capable of causing the clinical features of actinomycosis (q.v.) In nocardiosis the lesions, according to Weidman (Appleton's System of Med. 10 192, 1937) "usually resemble indolent furuncles of a sort which does not heal either spontaneously or under ordinary surgical treatment; the symptoms, resembling those of a gumma, are not so acute Occurring primarily on the thumb, the affection may extend as a line of gummas along the forearm so as to imitate sporotrichosis [like the case reported by Guy: ADS 2 137 1920]; only laboratory examinations can settle the diagnosis. In one case, there was brawny swelling around the ear; in another [Potron and Thiry: RevmédiEst 45: 159 193, 1913] a lesion on the neck resembled impetigo on the surface but a nodular mass lay underneath. Abscesses have been produced in the inguinal and lumbar regions by *N liquefaciens*, and *N gortezi* caused abscesses in the back and vertebrae. *N pedroensis* and *N fowleri* et al were found secondary to pulmonary disease. *N thibiergei* produced a subcutaneous gumma in addition to widespread lesions in the muscles. *N londinensis*, *N luteolus*, and *N krausei* may extend from the mouth to the subcutaneous tissues of the face. The symptoms may simulate deep ringworm, tuberculosis, actinomycosis or other fungous affections. The prognosis must be guarded, particularly in cases where there is deep extension, for there is the possibility of fatal generalization and death. If diagnosed early and treated with the iodides, there is hope for cure Iodide therapy is successful only when certain species of Nocardia are concerned: *N israeli*, *N liquefaciens*, *N gortezi* and, to a lesser extent, *N pulmonalis*. *N thibiergei* and *N asteroides* infections are resistant to iodide therapy Intensive iodide therapy combined with deep x-ray therapy and surgical evacuation of pus are advisable.

Sulfonamides, penicillin and other antibiotics are sometimes curative A case involving a child's foot consequent to a penetrating injury was identified histologically but not by cultures by Lamb et al. (ADS 67: 141, 1953) Pregnenolone was given orally in a dose of from 200 to 300 mg daily for 8 months, and cure resulted. The drug was chosen because it does inhibit *N asteroides* in vitro

See Davis (AIntM 14: 1, 1914); Pijper (MJSoAfrica 11 141, 1916), Christopherson and Archibald (Lancet 2: 847 1918); Gregor (J 79 812, 1922); Mason and Frost (CalifBJM 21 471, 1923); Foerster (AmJMedSci 167 54 1924) bibliography; Guy and Jacob (J 82 1862, 1924) cases following perforation of ear lobe; Pijper and Pullinger (JTropM, 30 153, 1927) mycetoma due to *N pretoriana* Guy and Helmbold (ADS 27: 224 1933), case, multiple gangrenous granulomas; Cutting and McCabe (AmJPath 25 1, 1949) case, abdominal lymphogranulomatous mass; Hager et al. (NEngJM 241 226 1949) *N asteroides* pneumonitis and empyema, cured with sulfadiazine, penicillin and streptomycin; Bernstein et al. (AnnIntM 36 852, 1952) 42 cases reviewed, resemblance to pulmonary tuberculosis, cerebral lesions, unresponsiveness to antibiotics. Hickey and Berglund (ArchSurg 67 381 1953) 5 cases cured with sulfadiazine, penicillin, Terramycin and appropriate surgery; Moore et al. (ADS 70 307 1954) ulcer near knee due to *N brasiliensis*

SPOROTRICHOSIS

Sporothrices are conidiospore fungi (Hyphomycetes) in which the conidia, simple or septate, hyaline or fuliginous, are discrete and are inserted directly into mycelial filaments. The conidia are mounted on a little pedicle (stipitate) in the genus Rhinocladium, a distinction Brumpt made in dividing Sporothrix into the two genera, Rhinocladium and Sporotrichum. Many of these fungi are of common natural occurrence, living as saprophytes; some of the species are able to parasitize man, animals and plants. There is good reason to believe that *Rhinocladium schenki*, isolated in the United States, is the same as *R. beurmanni*, isolated in France. Other pathogenic species include *R. dori*, *R. gougeroti*, *R. jeanselmei*, *R. indicum* and *R. councilmani*. See Schenck (BullJHH 9: 286, 1898) Cultural characteristics are given on p. 479

Symptoms.—Sporotrichosis is contracted generally by those who come in contact with the soil and shrubs, and infection follows some trifling injury such as the prick of a barberry thorn or the peck of a chicken I like Gastineau et al. (J 117 1074 1941) have seen numerous cases in florists. There was an epidemic involving several children in one part of Kansas City apparently contracted in a particular moldy trash dump

Clinical types of sporotrichotic manifestation have been classified in 5 groups by Lewis and Cudmore (AnnIntM 7 991, 1934) and Collins (ADS 56 523 1947)

Localized.—Most cases in the United States are of this group in which a primary lesion appears on an exposed part. The chancre is indurated, and softening and abscess formation may take place or an indolent ulcer or vegetation may develop. Rarely the disease remains localized but usually after a week or more, painless inflammation ascends the regional lymphatics, along which secondary nodules form. Regional lymph node enlargement is uncommon, a clinical distinction from tularemia. Systemic symptoms or involvement is uncommon. There

is little tendency for spontaneous recovery to occur After healing has been induced by treatment, scarring of some degree usually remains Localized warty cases, without subcutaneous infiltration or spread, are seen like that of Smith and Garrett (ADS 56: 532, 194)

Disseminated Gummatous.—Seen more commonly in France than in the United States, this variety is characterized by the appearance of small, hard, painless, subcutaneous nodules, various in number scattered over the body Within 3 to 6 weeks the overlying skin becomes involved, and the central part of the nodule softens to form an abscess, which may discharge if traumatized, forming a cup-shaped ulcer with an indurated border A lesion may continue indefinitely in the untreated patient.



Fig 38.—Sporotrichosis, showing ulcers which followed incision f lesions.



Fig 39 —Sporotrichosis chancre on fifth finger Lesions ha been incised, ulcers resulted (Dr G M Brown.)



Fig. 40 —Sporotrichosis characteristic lesions. (Drs. Arthur E. Hertzle and J M. Sutton.)

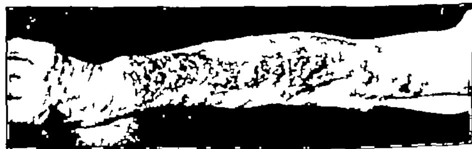


Fig. 741 —Sporotrichosis typical moniliform, noduloulcerati lymphangitis. (Dr T F Turner)

Disseminated Ulcerative.—Like the disseminated subcut neous type this I distinguished by a tendency to undergo early pontaneous ulceration. The ulcers are aried in size and character Large crateriform sores may develop simulating tuberculous lcers or gummatous syphilids. There is little tendency to heal spontaneously I treated, the patient graduall fails.

Epidermic.—While the primary lesion is practically always subcutaneous, rarely the epidermis at near or remote sites becomes secondarily infected, so that papules pustules and

small ulcers develop. In rare cases the disease has been limited to the skin. Tuberculosis is distinguished with difficulty

Systemic and Extracutaneous.—Invasion of deep tissues and organs may occur This happens in disseminated cases when treatment is not instituted promptly The bones & joints may be affected, the tibia being the commonest site. Invasion of muscular and glandular structures may occur and evidence of pulmonary involvement have been reported. Although the epididymis is the common site of involvement in laboratory animals, it is rarely affected in human beings. Gastrointestinal and cerebrospinal infections are extremely uncommon.

Diagnosis.—It is next to impossible to demonstrate the mycelium or conidia in direct smears, but the parasite grows readily on ordinary culture media Tissue diagnosis is not definitive for the lesions simulate those of syphilitic tuberculous or ecthymiform pyogenic infection. Odd clinical examples were described by Smith (SouthMJ 38 505 1945) manifested by pustules, plaques or lesions like bromoderma. Suspicion of the disease should be ever-present and cultural diagnosis is essential (Moore and Manting ADS 48: 525 1943) Asteroid bodies, as are seen in sarcoid are present in some cases (Moore and Ackerman ADS 53 253 1946 Pinkus and Grekin ADS 61 813 1950) The lymphangiitic type in which the row of nodules follows the



Fig. 742—Sporotrichosis, unusual (Dr Leslie M Smith.)

lymph channels draining a traumatic lesion that has proved resistant to ordinary treatment, is almost pathognomonic clinically An agglutination test, using as antigen the spores obtained by filtering the 4- to 12 week-old colonies through cotton, is specific in dilutions as great as 1:4 000 (Weidman Appleton's System of Med., 10 184 1937) and an intracutaneous test with sporotrichin, analagous to the trichophytin test can be performed but these diagnostic methods are not so practical as cultures.

Prognosis and Treatment.—Iodide given internally in the form of sodium or potassium salts, and iodine locally as the tincture or diluted as Lugol's solution, are almost specific. Surgical intervention generally retards cure rather than hastens it Roentgen therapy locally is not successful Potassium iodide should be given by mouth in doses of from 2 to 6 Gm. a day and should be continued for a month after apparent recovery which requires something around 10 weeks. When iodide by mouth does not reach a concentration that is efficacious, concomitant intravenous medication often succeeds. Sodium iodide is given intravenously in doses of from 15 to 30 grains (1 to 2 Gm) dissolved in 20 cc. of water daily if necessary A patient of Dwyer's (pers. comm., 1959) intolerant of iodide was able to take the drug when given cortisone also Sulfonamides penicillin and streptomycin are not effective





Fig. 743.—Sporotrichotic gumma. (Dr. D. [illegible].)
Fig. 744.—Sporotrichosis, localized, of nose. (Dr. O. G. Costa.)





Figs. 745 and 746.—Sporotrichosis, systemic. (Dr. Grover W. Wende.)

See Wolbach et al. (JMedRes 36: 337 1917) *S. councilmani*. Foerster (J 87: 1605, 1926) sporotrichosis as an occupational disease. Pijper and Pullinger (Lancet 2 914, 1927), South Africa cases. Lawless (ADS 22: 381, 1930) complement fixation and skin tests; Downing (NEngJM 212: 1088, 1935) boy finger; Moore and Kile (ADS 31: 672, 1935) disseminated gummatous case, *S. beurmanni*. Loew (J 107 1040, 1936) neck gland, hard to recognize. Montgomery and Holman (PWSIMO 13: 466, 1938) hand case simulating cancer; Graham (ADS 43: 308, 1941) gumma, wrist; Hay and Rockwood (ADS 46 211, 1942) case unresponsive to iodide. Costa (BrasMed 57: 324, 1943) Brazilian cases. Noojin and Callaway (ADS 49, 308, 1944) No. Carolina cases, 1% sulfanilamide inhibits cultures. Costa and Junqueira (ADS 51: 261 1945), papular on nose. Salvin (JID 9: 318, 1947) multiple budding in *S. schenckii*. Smith and Garrett (ADS 56 53, 1947) verrucose case. Robinson (SouthMJ 42 343 1949) 3 Baltimore cases from handling fertilizer; Thomas et al. (J 147: 1342, 1951), case improved with hyperthermia. Silva (ADS 65: 385, 1952) acneiform cases in Colombia, Castleton and Rees (J 148 541 1952), Salt Lake City cases. Weichardt (AfDuS 192 236, 1951), periurethral abscess; Singer and Muncie (NYSJM 52 2147 1952) flower bulb farm cases and 1 from a cat. Carrión (AD 72 523, 1955) *Sporotrichum gougeroti*, with black colonies, is not a Sporotrichum but perhaps belongs with the genus [illegible].





Fig. 747.—Sporotrichosis lesions, culturally proved, limited to the hand (Dr Grover W Wende.)

Fig. 748.—*Sporotrichum schenckii* culture on glucose agar 5 weeks old. Color 1 pale brown, becoming deep brown. (Dr F D. Weidman.)

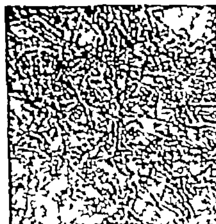




Fig. 749.—*Sporotrichum schenckii* culture. (Dr F W Shaw)

Fig. 750.—*Sporotrichum schenckii* hanging-drop culture showing trefoil clusters of stipitate conidia. (Dr F D. Weidman)

HISTOPLASMOSIS

Histoplasmosis, caused by *Histoplasma capsulatum* is an infection characterized by irregular pyrexia hypochromic anemia, emaciation, and enlargement of the liver spleen and lymph nodes (Conant et al. Manual of Clinical Mycology Saunders, 1948) Ulceration of the oral mucosa, especially the tongue and of the pharynx and larynx occurs frequently (Parsons and Zara

fonetis ArchIntM 7o 1 194o) In his original description of the disease Darling (J 4C 1283 1906) noted its resemblance to kala azar Lymph node involvement may simulate Hodgkin s disease Bone marrow involvement accounts for the anemia Diagnosis is accomplished by *identification of the organism* in biopsies but the skin test probably is specific (Pernis et al. J 117 436 1941) The frequency of asymptomatic positive reactors suggests that many an infection like coccidioidomycosis is subclinical.

Of the 12 actual and 3 possible cases of cutaneous histoplasmosis collated by Curtis and Grekin (J 134 1217 1947) 13 had granulomatous or ulcerative lesions, 3 showed nodular lesions 3 had papulonecrotic lesions and 2 had abscesses. In 10 cases the cutaneous lesions were distributed over the face and neck and in C of these they were adjacent to the orifices. Lesions were present on the trunk in 4 cases the extremities in 4 the male genitalia in 2, and generalized in 1 Of 19 cases of histoplasmosis of mucosae adjacent to the skin 7 were granulomatous and 1C were ulcerative usually very painful. Nodules ranging from several millimeters to walnut size were described in 5



Figs 781 783 —Histoplasmosi the man tongue in January, 1944 4 months later and the organisms in a section. (Dr F M Keddie)

cases, hemorrhagic patches or crusts of various sizes were noted in 4 cases, fissures in 2 and perforation of the nasal septum in 3. Lesions were present in the nose in 4 instances, on the tongue in 7 on the buccal and labial mucosae in 5 palatal in 5 gingival in 3 and hypopharyngeal in 7

In a review of 88 cases Miller et al. (ADS 36: 15 194) noted that the lesions f hi toplasmosis may resemble those of tuberculosis syphilis, the deep mycoses, or lymphoblastomas, and that the systemic disease must be distingui hed from kala azar malaria, dysentery and cancer The cyt logically non pecific hronic infect ous granulomas contain macrophages a their la lo reacting cells, and this nflammation may produce ulcers and gummas of the mouth, papules, plaques a l punched-out ulcers, purpuric lesions abscesses a d furunculoid or impetiginoid lesions, localized or general zed.

It is probable that the large majority of infections are a ymptomatic at the onset r are featured by unrecognized upper respiratory illness There are analogies to coccidioidal infection (q.) wherei nly a few i d viduals manifest disease which, more often the affecting the ki ffect the lu gs and mediastinal nodes, giving rise to roe tgenographic abnormal ties difficult to dist gu sh from tuberculosis. The epidemiology of the disease ha for some time been unde the careful scruti y of Furcolow (see ref reare) f the U.S.P.H.S. at the University of Kansas Medic l Center in a region where the infection is endemic and where the organisms have been found in farmyards and chicken houses. Positivity of the

skin test must be interpreted much as tuberculin tests are interpreted, the incidence of positive reactors increasing with the age of the tested subjects and reactivity not being proof of activity of disease.

An "id" eruption occurs in histoplasmosis which simulates the papulonecrotic tuberculid. The lesions are disseminated, occur in crops, affect especially the extremities, and are inflammatory papules which undergo central necrosis and ulceration, healing with atrophic scars.

The similarity to pityriasis lichenoides et varioliformis is so suggestive that careful investigation of cases so titled should be made from this standpoint. I surmise that "parapsoriasis varioliformis" may be a manifestation of histoplasmosis.

Treatment hitherto has been ineffectual with reports indicating that the diagnosis of histoplasmosis meant death within 8 months. Stilbamidine and related chemical substances appear to offer great promise in suppressing or eliminating the disease (Furcolow).

See Hausmann and Schenken (AmJPath 10: 731, 1934), papular lesions with crateriform ulceration, 16-year course leading to death; Shaffer et al. (J 113: 484, 1939) fourth U. S. case, review; Amolsch and Wax (AmJPath 15: 477, 1939), tenth case, infant with cough, leukopenia, fever, weakness; Gunter and Lafferty (AlaMJAJ 9: 337, 1940) headache, fever, necropsy; Brown et al. (PMDIO 15: 612, 1940) oral ulceration, fatal dissemination; Rhodes et al. (JPediat 18: 228, 1941) infant with an ulcer, enlarged liver and spleen and purpura; Palmer et al. (ADS 46: 912, 1942) throat first, scattered ulcers, death; Moore and Jorstad (AnnOtol 52: 779, 1943) oral; Broders et al. (J 122: 489, 1943) ... endocarditis; Kemper and Bloom (JOralSurg 2: 167, 1944) oropharyngeal, then disseminated; Kedall (ADS 53: 130, 1945) tongue involved, Hodgkin's disease also present. Palmer (PHRpts 60: 513, 1945), pulmonary calcification cases without tuberculosis but with reactivity to histoplasmin. Furcolow (PHRpts 63: 759, 1948; 65: 965, 1950), 10 cases of histoplasmosis without tuberculosis, 1 death from periarteritis nodosa and multiple granulomas of undetermined cause. Furcolow (PHRpts 62: 1711, 1947; 64: 1363, 1949) relation of calcified pulmonic lesions and histoplasmin reactivity; Loosli et al. (AmJHyg 53: 33, 1951), epidemiology of histoplasmin sensitivity; Furcolow and Grayston (Trans 48th meeting, Natl TBC Assn 1952) review of 12 epidemics, isolation of organism from soil at 10 point-source epidemics. Grayston and Furcolow (AmJPubH 43: 665, 1953) inhalation epidemics. Nilsen and Paldrok (ActaD-V 33: 329, 1953) 7 bronchopneumonic cases contracted by laboratory workers.

MISCELLANEOUS AND UNCOMMON MYCOSES

Acladiosis.—Conidiospore fungi of the genus Acladium have been found in cases characterized by scattered ulcers, sharply defined, round or oval, with red and granulating bases, abundant purulent secretion and thick yellow crusts, lesions which were gummalike as well as furuncular located on the palms and soles or elsewhere. The disease is chronic without tendency to heal spontaneously. It is responsive to iodide therapy. It is identified only by cultural study.

Acremoniosis.—*Acremonium potroni* has caused typhoidlike fever and gummalike swellings which underwent ulceration, but without lymph node involvement. Other cases have resembled mycetoma with yellow grains.

Aspergillus and Penicillium.—These genera of Ascomycetes bear conidia in chains arising from specialized cells called phialides. They are moldlike fungi. Several species have been thought to act as parasites and to have caused mycetomas, infections of the lungs and superficial infections of the ear canals, nasopharynx, skin and cornea. They are found commonly enough as saprophytes on crusted, dirty dermatoses, and one must be critical, though not incredulous, of reports of their pathogenicity. Allergists are obliged to take them seriously as sources of inhalant difficulties. See Otomycosis and Onychogryposis.

Cephalosporiosis.—Cephalosporium is a genus of the sporophore division of the hyphomycetic fungi. The organisms, of which there are several species, have produced nodular gummatous lesions and dermatomycoses of varied clinical appearance. Diagnosis depends on the demonstration of the fungus and its identification. These infections in general simulate sporotrichosis and are responsive to potassium iodide and roentgen therapy.

Cladosporiosis.—Cladosporium is a genus of dermatophytes, species of which have produced nodular gummatous inflammations and dermatomycoses unresponsive to iodide. Diagnosis depends on cultural identification.

Geotrichosis, productive of chronic bronchitis with gelatinous sputum or pulmonic disease simulating tuberculosis, may affect the oral mucosa in white patches distinguished from thrush simply by direct examination of scrapings, which reveal characteristic rectangular spores (Brumpt 1949 p. 1742).

Hemisporosis.—Hemispora include hyphomycetic fungi which reproduce by accessory spores or hemispores. Species have been found in cases which resembled sporotrichotic infections and like them were responsive to iodide therapy (Brumpt 1949 p 1801). Osteoperiostitis, generalized nodular eruptions, and gummatous sores with tuberculoid histologic structure have been attributed to Hemispora (Castellani and Chalmers, 1929 p 2106).

Mucormycosis.—Mucormycosis has been diagnosed in paronychia of orange workers by Sutherland-Campbell and Plunkett (ADS 20 651 1934), in otomycosis and in furunculoid lesions of the face by Wade and Matthews (J 114 410 1940 see Mezey J 114 1098, 1940). The 3 cases of Pirila (ActaD-V 28 186 1948) exhibited pustulation with suppurative lymphadenitis and cleared spontaneously in a few weeks uninfluenced by treatment.

Rhizopus, identified by the histologic finding of huge nonseptate mycelium in the central granulomatous masses as well as in the advancing borders of the lesion, apparently caused a curious lesion of a boy's chest (Englander ADS 68 741 1953). The lesion clinically showed a reticulated and atrophic center and a border composed of active lichenoid papules. Therapy was without avail until excision was performed and this cured the patient (Goldman told me (1956)).

Scopulariopsis.—This is a genus of the Ascomycetes related to Penicillium, the conidial apparatus being similar. Species have been isolated in a case resembling sporotrichosis with verrucous chancres and ascending lymphangitis, in onychomycosis and in ulcerative mycetomas and gummatous lesions (Markley ADS 33 627 1936). The curious case presented by Hall (ADS 54 173 1946) had lesions suggestive of hypertrophic lupus vulgaris; this patient improved markedly on potassium iodide by mouth and x ray therapy. See Castellani and Chalmers (1929 p. 2107) Brumpt 1949 p 1978).

Sterigmatocystis.—Superficial eczematous and epidermal disease has been attributed to perhaps purely saprophytic fungi of this genus. *S. cinnamominus* was found in a Peruvian case resembling tinea versicolor. Species have been found in the ear canals. A black grain mycetoma was described by Pinoy as being due to *S. nidulans* (Brumpt 1949 p 1967).

Allescheria.—See Pinoy (JMIJ 2 488, 1919). Castellani and Chalmers (Tropical Medicine ed 3 1929 p [illegible]). Castellani and Jacono (JTropM 3 [illegible] 1934) keratitis case simulating [illegible] paracladiosis described.

[illegible]—See Potron and Noisett (Rev méd de l'est, 43 [illegible] 161, 1911). Castellani and Chalmers (Tropical Medicine ed 3, 1929 p. 106). Brumpt (Précis de Parasitologie Masson, 1949 p. 1824).

Aspergillus [illegible]—See Castellani and Chalmers (Tropical Medicine 1929 p. [illegible]). Wilson (JJTech 72 1 1933) cases. Hilgermann (ArDuS [illegible] 393, 1935) role in eczema. Brown (JAllergy [illegible] 488, 1936) role in asthma due to dust. [illegible] Simon (J 110 440 1938) [illegible] Sharp (JID 4 208, 1941) a [illegible] from mold. Thom and Raper (M[illegible]al of the Aspergilli, Williams and Wilkins 1945) botanical monograph. Morris (R[illegible] 104 116, 1946) [illegible] mycology. Dresser [illegible] Graham (CalifM 66 [illegible] 191) respiratory [illegible] especially of Alternaria and Hormodendrum. Brumpt (Précis de Parasitologie Masson, 1949 Aspergilli (p 1952) Penicillium (p. 1974).

[illegible]—See Oonen (NederlTijdschr Geneesk 81 3639 1937) case with beard, hand, nail [illegible] and renal calculus found at autopsy with organism growing on it. [illegible] Jank (ArDuS 188 35 1949) [illegible] Brumpt (Précis de Parasitologie Masson, 1949 p. 1977).

Cladosporium.—See [illegible] (ComptrendAcadSc 152 412, 1911). Castellani and Chalmers (Tropical Medicine 1929 p 210[illegible]). Brumpt (Précis de Parasitologie Masson, 1949 p. 1823).

DERMATOSES DUE TO ANIMALS

Craig and Faust (Clinical Parasitology Lea & Febiger 1951) and Brumpt (Précis de Parasitologie, Masson, 1949) are the principal authorities used in the preparation of the chapter Valuable also are Riley and Johannsen (Medical Entomology McGraw Hill, 1938) Stitt and Strong (Tropical Diseases, Blakiston 1942) Culbertson (Immunity Against Animal Parasites, Columbia Univ Press, 1941), Ash and Spitz (Pathology of Tropical Diseases, Saunders, 1945) Chatt rjee (Human Parasites and Para itic Diseases, Calcutta, 1953), Brown (Synopsis of Medical Parasitology V E. Brown, Milwaukee, 1953) Piekarski (Lehrbuch der Parasitologie unter besonderer Berücksichtigung der Parasiten des Menschen, Springer 1945) Kudo (Protozoology Thomas, 1954) and Hackett et, al (Manual of Medical Helmi thology Carsell & Co. 1954)

PROTOZOA

AMEBIASIS

Endamoeba histolytica is a rhizopod protozoon manifesting trophozoite precystic, cystic, and metacystic stages in its life cycle. In unstained preparations the trophozoites range from 15 to 60 μ in diameter averaging about 20 μ. The exoplasm is glassy clear the endoplasm finely granular and the nucleus almost invisible. Exoplasmic pseudopodia are rapidly and actively extruded in freshly passed stools, but motility is sluggish in cool preparations. The habitat is the distal gut, and transmission is accomplished by ingestion of substances, usually a polluted water supply contaminated with feces containing cysts of the parasite. Asymptomatic carriers exist.

Symptoms.—Cutaneous involvement may be classified as occurring by ex tension, by inoculation, and from allergy (Touraine and Duperrat PresseMéd. 47: 1086 1939) Extending in the skin following surgical attack upon an amebic visceral abscess, amebic dermatitis is ulcerative starting within 1 to 3 weeks as a rule with a little redness and developing black necrosis or furuncu lar anthraxlike lesions. Perianal extension of colonic and rectal disease oc curs. Inoculation with purely cutaneous amebiasis is rare, the lesions being extensive ulcers or sometimes circumscribed torpid abscesses which crust, ex tend peripherally, and heal with scarring Genitalia of male or female may be inoculated. Allergic dermatoses dependent on amebiasis include anal pru ritus, urticaria, rosacea like disease buccal melanosis and desquamative ery thema from emetine or other medicines. Amebic ulcers in the skin generally are large circular ragged, purulent lesions, with deep red undermined swol len edges. Diagnosis requires positive identification of the organism.

Treatment with emetine a hazardously toxic alkaloid from ipecac, is usu ally successful the hydrochloride being given in 0 065 Gm (gr i) doses sub-cutaneously for 10 (not more than 12) doses in a course (Kreutzer Surg 29: 149 1951) Chiniofon (Yatren) Diodoquin, Vioform and carbarsone are also effective (see Craig and Faust)

Aureomycin was fou d to be effective by McVay et al. (Sci 109: 590, 1949; SouthMJ 43 303, 1950) and of 37 cases treated, 36 were apparently cured with 2 Gm. daily for 7 days. Aureomycin cured cases previously recalcitrant under Diodoquin, carbarsone and even emetine, reported Hughes (J 142 1032, 1950) The recurre ce rate after the anti-biotic compared favorably with that following othe drugs, wrote G tch (NEngJM 243: 165, 1950) while Hall (NEngJM 244 495, 1951) thought it especially effecti e in treating carriers. Gut, liver and belly perforations all respond to Aureomycin, said McVay and Sprunt (SouthMJ 45: 182, 1952), and pparent failures are often attributable to reinfection from a member of the immediate family of the patient.

Emetine, carbarsone and chiniofon combined gave an excellent initial response and a moderate relapse rate; but Terramycin alone and in combination with (1) emetine, (2) carbarsone, (3) chiniofon, (4) chloroquine diphosphate, and (5) bismuth glycolylarsanilate a d chloroquine, and the combination of Aureomycin and chloroquine diphosphate all gave excellent initial responses and the lowest relapse rates observed by Martin et al. (J 151: 1055, 1953) The combination of bismuth glycolylarsanilate and chloroquine in the proportion of 500 mg to 150 mg. was the most effective amebacide disclosed by the compara tive studies of Sanchez (J 151: 1069 1953)

Fumagillin an antibiotic introduced by Hanson and Eble (JBact 58: 527 1949) was shown to be amebicidal by McCowen et al. (Sci 113 202, 1951) Its essential lack of toxicity and its effectiveness against several enteric protozoon parasites, including *E histo-*

lytica were reported by Killough et al. (Sci 115 71 105) Effectively curati e in amebiasis, fumagillin in luced a triking Ile effect of exf llation of palm and soles in of 3 cases of Schindel (J 155: 903, 1054) a well as some sensory an l auditory neuriti

Ngal and Frazier (ChinMJ 4 : 1184, 1933) 7 cases, ri les. Shih et al (Chi MJ 53 139 1939) corneal ulcus l ol ed; M leney (J 103: 1212, 1931) lcers about sinus tracts from drai ing pi nilt or colonic ulcer J rnst d and Launey (T xasMJ 37: 713,



Figs. 784 and 85.—Amebiasis l of ing perian l kin f a Chinese with amebic coliti Fig 84 before treatment Fig 85, aft tment of i testinal dis se with metine (Ngal nd Fra ie ChinMJ 47 1184 1933



Fig 786—Amebic dermatitis section showing meba t the dermo-epidermal junction and also within the epidermis nd acut purulent inflammation in the dermis. (Ngal nd Frazier ChinMJ 47 1184 1933)

1942) bdominal wall in ol ed from li er bsces Hermans and Herman (J 120 837 1942) penile ulcer Cleland (JTropM 47 64 1944) ameba present in exten l gra uloma inguinale of pudenda Craig (Etiology Di gnosis nd Treatment of Amebia is, Williams & Wilkins 1944) Wilson and Hurewit (MClinN Am 30 411 1946) perianal Morton nd Foster (BMJ 2 996 1947) buttock bscess with sin Sen (BMJ 1 808, 1949) anal ulceration; Emmett (J 141 22 1949) slough er bscess of liver cured by chloroquin 0 5 Gm. per day for 10 days Nowicki (J 150 812, 1952) necrosis and lceration of foot due to ameba in Venezuela Faust (Amebiasis, Thomas, 1954) monograph.

TRICHOMONAS VAGINITIS

The class Mastigophora, flagellate protozoa, includes the Trichomonadidae, of which *T vaginalis* is associated with mucosal disease of dermatologic interest. The organism is pear-shaped, about 10 μ long and possessed of 3 to 5 anterior flagella. The marginal filament along the undulating membrane is not prolonged into a free flagellum and there is a well-defined parabasal body Pathogenicity has not been positively demonstrated.

Symptoms.—While many women harbor the organisms, comparatively few complain. Vulvar pruritus is sometimes attributed to them. Redness, excoriation, edema, pinpoint vesicles and minute caruncle-like lesions were described by Hollander (ADS 36 142, 1937) Kessel and Gafford (AmJOG 30: 1005, 1940) recorded histologic changes, finding trichomonads in acute inflammation with focal necroses; their implants of exudate into normal vaginas produced the disease but implants of cultures did not. Leukorrhea may be profuse and is typically alkaline It is grayish-white seropurulent, and peculiarly foamy when the speculum is introduced. Symptoms tend to be cyclic the exacerbations overlapping the period of menstrual flow Difficulty in eradicating the infection often depends on the presence of rectal, urethral and glandular involvement or on reinfection (Trussell Trichomonas Vaginalis and Trichomoniasis, Thomas, 1947) In the male, preputial and prostatic involvement may be present.

The organisms are readily demonstrated on microscopic examination of a hanging droplet of saline to which exudate has been added. An intradermal test with trichomonas antigen was evaluated by Adler and Sadowsky (Lancet 1: 867 1947) as being of no practical value

Treatment.—Insufflation of the vagina twice a week is effective using a powder containing acetarsone 1 parts, salicylic acid 2, and sodium bicarbonate and kaolin in equal amounts to make 100. The vaginal pH should be kept less than 5 by means of lactic acid douches, a dram to the quart of water which should be used twice a day between periods and three times a day during the menses Hugh Hamilton advises. Acetarsone one grain to 5 cc. of water is an effective and acidic parasiticide for intravaginal treatment (Karnaky: AmJSurg 35: 17 1940) Reich et al. (SGO 84: 891 1947) advised vinegar douches and a gelatin capsule insert containing Argyrol, kaolin and betalactose powder Insufflation of quinacrine powder into the carefully cleansed and dried parts was advocated by Dula (NCarolMJ 9 309 1948) A reomycin by mouth cured the infection in a male reported McV and Sprunt (SouthMJ 44 1122, 1951) Terramycin used in vaginal suppositories seemed effective to Green (aha J 149: 1060 1952)

LEISHMANIASIS

Among the protozoa, those which move by means of flagella comprise the class Mastigophora. *Leishmanias* form a genus of Trypanosomidae the family which includes all flagellates living in the blood and tissues of human beings. Leishmania have vertebrate and invertebrate host and, in their life cycle, a leishmania and a leptomonas stage. In the human host is found the typical leishmania, with ovoid body containing a nucleus and kinetoplast, the latter giving rise to a single flagellum in the invertebrate host. Reproduction occurs by binary fission. The 3 species recognized as infecting man are morphologically identical despite the different clinical pictures produced by them. They can be differentiated on the basis of serologic reactions (Noguchi: JExperM 44: 327 1926) *L. donovani* causes visceral leishmaniasis, or kala-azar *L. tropica* causes cutaneous leishmaniasis, or oriental sore. *L. brasiliensis* causes American leishmaniasis.

Oriental Sore is a specific, ulcerative disorder which usually develops on the leg face or other exposed part of the body A small sore appears at the site of the bite of an infected sand fly *Phlebotomus papatasii* and the reddish papule increases gradually in size. After a number of months it becomes bluish in the center softens and ulcerates. The number of lesions ranges from 1 to 17 most often from 3 to 8 single sores are rare The sore is not accompanied by adenopathy After a duration of several months or even a year an untreated ulcer undergoes cicatrization and leaves a characteristic stellate scar Permanent immunity eventually results (Behdjet abs YBD 1937 p 192) but superinfection with *L tropica* proved possible despite positivity of the leishmanin intradermal reaction, noted Dostrovsky et al. (ADS 66 665 1952) who observed that immunity does not suffice to prevent this, and that circulating antibodies cannot be demonstrated

Three clinical forms were classified by Marchionini (Dermatologica 97: 319, 1947) in a review of some 800 cases from Ankara: the local sore inoculated by the bite of the sand fly the metastatic sores from hematic or lymphatic dissemination resembling lupus erythematosus or lupus vulgaris; and the disseminated nodular variety which showed no tendency to heal spontaneously He recommended Atabrine or locally injected antimony



Fig 757.—Ori[illegible] sore (Dr [illegible] M [illegible]wen.)



Fig [illegible].—Oriental sore [illegible] (Dr [illegible] Aragão.)





Fig 759.—Tropical granuloma. (Dr F G Harris.)
Fig 760.—Oriental sore (Dr C. L. Pickett.)





Fig 761.—Verrucose leishmaniasis, Brazilian case, a rare type. (Dr O G Costa.)
Fig. 762.—Leishmaniasis in a Pekin mongrel. (Feng et al. ChinMJ 55 371 1939.)

preparations in treating local cases, while the metastatic form required, he believed, an antimonyl given for its systemic effect, such as Solustibosan in doses of from 3 to 4 cc. daily for 10 days, accompanied by supportive hygienic measures.

Experimental inoculations reveal an incubation period of from 16 days to many months, depending on quantity and depth of the inoculum and on the degree of individual susceptibility reported Berberian (ADS 49: 433 50: 231, 233 234 1944) A vaccine from the cultures of *L. tropica* may have some preventative value and the intradermal test has some diagnostic value After experimental inoculation the skin test remains negative for about 3 days, then becomes positive (Dostrovsky: JID 10: 435 1948)

Diagnosis by means of positive cultures was recommended by Pachchanian (J 129: 544 1945) using ordinary blood agar slants, and cultural diagnosis seemed easier than the demonstration of parasites in smears, according to Dostrovsky and Sagher (ADS 54: 543, 1946)

Principal pathologic changes are in the dermis. The histologic picture is not distinctive except that it is tuberculoid. The presence of Leishman Donovan bodies, representing the specific parasite readily demonstrable as a rule in a Giemsa stained preparation, is diagnostic.





Fig. 163A —Nodules of leishmaniasis (Dr O. G. Costa.)
Fig. 163B —Spina ventosa of phalanx, due to leishmaniasis. (Dr O. G. Costa.)

The malady is self limited, although its duration can be greatly shortened. Local treatment with wet applications and iodine help and specific treatment with ½ grain potassium antimony tartrate in 5 c.c. water intravenously on 1 day followed 3 days later with 1 grain and continuing with 1.5 grains a week, led to cures (Goodall: IndMGaz 72 2, 1937) Snow et al. (ADS 57: 90 1948) spoke highly of Neostam in treatment but Most and Lavietes (Med. 26 221 1947) preferred ethylstibamine (Neostibosan), giving 0.3 Gm. intravenously daily for 17 days. Treatment failures may be retreated with larger doses, or with stilbamidine.

See Altounyan (JCut&VD 3 161 1885) Wright (JMRes 5 472, 1903) original description of *L. tropica* Andrews (AmJTropM 7 231, 1927) 10 cases in North America; Hasch-khilelsson et al. (AnndeD 6: 210 1935) resemblance to tuberculosis cutis Ray (IndianJPediat 2 149, 1935) acne therapy; Hupoumenakis (ArDerS 178 183, 1938), comparison of oriental sore and kala-azar organism of latter is motile, of former nonmotile Flarer (PresseMed 46 1338, 1938) Atabrine locally and internally to cure; Derim (ADS 41: 874, 1940) recidive and id forms; Templeton (CalifWM 54 76 1941) experimental inoculation; Dostrovsky and Sagher (ADS 48 668, 1943) grenz ray therapy Kozhevnikov (see ADS 48 476, 1943), in U.S.S.R.; Katzenellenbogen (ADS 50: 239 1944) preventative vaccination; Hall and Ryan (BullU.S.ArmyMD Aug. 1944 p. 65) Middle East cases and description Gill (ADS 54: 331, 1946) Palestine cases Conrad et al (ADS 62: 501, 1950) 4 cases, discussion of treatment.

American Leishmaniasis, due to *L braziliensis* differs from oriental sore in its varied and longer course, its failure to produce immunity the involvement of the nasopharynx in from 10 to 20% of the cases, its greater resistance to treatment, and its causation at times of cachexia and death Oriental sore is a milder disease, confined to the skin, responding readily to treatment. See Fox (ADS 30 241 1934 J 123 461 1943) Two clinical forms may be dis-



Fig. 764.—Nasal polyp, leishmaniasis. (Dr. O. G. Cost[illegible].)



Fig. 765.—Mucocutaneous leishmaniasis. Ulcerati lesion. ([illegible] et al.: Clinical Tropical Medicine, Mosby, 1951.)

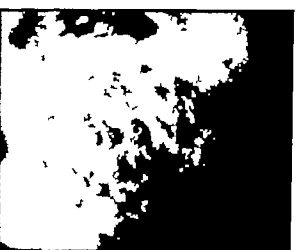
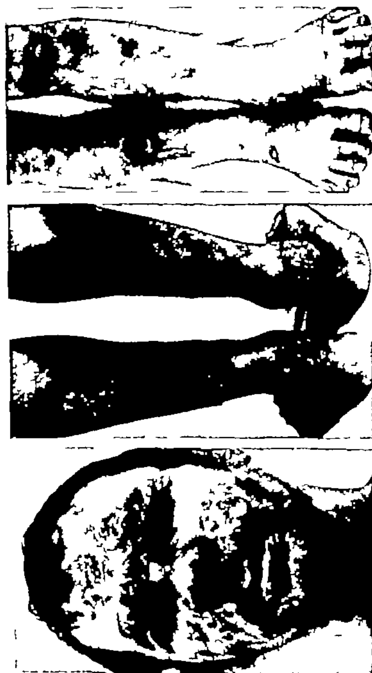


Fig. 766.—Leishmaniasis nodularis. ([illegible] 51: 333, 1946.)



Figs. 767-769.—Leishmaniasis, Brazilian cases. (Dr. O. [illegible])

tinguished, uta resembling oriental sore and occurring in the arid valleys of the Andes where verruga peruana is endemic, and espundia, a more serious disease involving adult patients rather than younger ones, affecting the mucous membranes, and occurring especially in sylvan regions among persons working in forests and on cacao and tea plantations (Weiss abs YBD 1944, p 305)



Figs. 770-772 —Leishmaniasis, Brazilian cases. (Dr O. G Costa.)

Uta is endemic in limited areas, shows a predilection for children under 4 years of age, runs a benign course, and produces immunity The initial lesions are usually found on uncovered parts of the body never on the scalp or keratotic volar skin. At the beginning they resemble mosquito bites, but become papular and eventually nodular Ulceration may ensue, and impetiginoid, ecthymatous and ulcerous varieties may be distinguished.

Vesicopustules located superficially may become confluent crusted and of a diameter reaching 10 cm., or ulceration ma be less superficial or gummatous sometimes actually phagedenic N nulcerated cases ar also seen sometimes simulating keloid, though without a smooth surface Veg tative form occur too, verrucose or yaw like



Figs. 773 775.—K la-asa nod les nd bpleme tel lesions in nati Indi ns. (S pler 1 Daal pt 1 In IMG n 69 1 1 1924)

Espundia frequently begins around the nasal septum or in othe parts of the upper respiratory mucosae spreading more rapidly than the cutaneous forms, i vasive of the whole extent of the upper passages and even involving, sometimes, the pharynx, larynx and trachea. In the mouth there is predilection for the palate checks d mucosae of the cheeks, but seldom is the tongue involved. Palat l lesions are more often proliferative

than destructive and the resultant granulation tissue may resemble that of blastomycosis. The lesions interfere with respiration and feeding, and marasmus and death eventuate sometimes from edema of the glottis or an acute pulmonary complication.

Regional lymphangitis is common, is often nodular and generally is painful (Kean: ADS 50 237 1944). Ulceration of the pinna is common among workers who collect gum, and bears the name "chicle sappers' ear" (oreja de chicleros). Mutilating and ulcerative lesions of the mouth and nose occur in perhaps 20% of the cases in the moist, tropical regions of Peru (Schmidt: ADS 61: 984 1950).

Treatment with 2 hydroxystilbamidine, 225 mg in 200 cc. 5% glucose given intravenously daily to a total dose of 6.1 Gm. cured a patient without intoxicating her (Snapper AmJMed 13: 6.. 1952).

See McEwen (JCutDis 32, 275, 1914) description and bibliography; Wenyon (JTropM 14 103, 1911) parasitology; Mehrdorf et al (JUD 38 231, 1920) espundia contracted by Briton in Brazil; Fox (ADS 23 480 1931 30 341 1934; J 123: 461 1943); Dostrovsky (AnnTropM 29 123, 1935) intradermal test; Shattuck (AmJTropM 16 187 1936) epidemiology; da Cunha and Dias (abs J 113 1998, 1939) complement fixation test; Humphreys (AnnTropM 36 3 1943) treatment with Pentamidine, diamidine derivative; Costa (ADS 49: 194 1944) Brazilian cases; Stewart and Pilcher (ADS 51 124, 1945), Texas case; Costa (ADS 55 358, 1947), erroneous case; Cornejo and Llanza (quoted J 138 1169 1948), clinical forms, treatment with stibophen, chiniofon, antimony; Hasslins and ll er Cordero (ADS 62: 428 1950) unusual case, Repodral treatment.



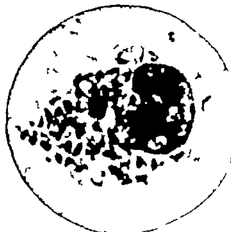


Fig. 776.—*Leishmania donovani*, flagellated forms seen in cultures. (Army Medical Museum photomicrograph, from Meakins' Practice of Medicine, The C. V. Mosby Co.)

Fig. 777.—*Leishmania tropica* in a smear from tropical ulcer. (Army Medical Museum photomicrograph, from Meakins' Practice of Medicine.)

Kala-Azar.—This severe form of visceral leishmaniasis occurs in parts of India, China and the Sudan. It is a localized disease which may attack all the persons in one dwelling or group of dwellings and leave unaffected persons only a short distance away. All races and both sexes are infected. *Phlebotomus argentipes* is a vector, the bite or perhaps the crushed body serving to inoculate. After an incubation period of several weeks, kala-azar is manifested characteristically by an irregular fever lasting for months, uninfluenced by quinine, with hypertrophy of the spleen and liver. In advanced cases, numerous ulcers occur in various places along the digestive tube, such as gangrene of the mouth, or ulcers of the nose or of the large intestine, and on the skin. Wasting becomes advanced, contrasting with the protrusion of the belly which is likely to be distended with ascitic fluid. Cutaneous lesions, leishmanids, contain parasites. On the skin of the body, limbs, or face appear depigmented zones, erythema, nodules, or more rarely verrucous, papillomatous lesions resembling those of xanthoma, with perhaps thickening of the lip, eyelids, and alae nasi. Evolution is insidious and may cover a period of 10 to 30 years. Cutaneous disorders are considered sequels of kala-azar, supervening in some instances in subjects who are ignorant of having had the malady. They may be mistaken for leprosy. Marked leukopenia, even to levels below 1,000 leukocytes per c.mm., is characterized in the blood picture, the reduction

of the polymorphonuclears being especially marked. The main visceral lesions involve the spleen liver and large intestine The tissue of the spleen is firm but friable and macrophages with parasites in them are found here diagnostic on splenic puncture Sternal puncture is a safe way to obtain diagnostic material

See N pier (IndJMR 21 830, 1922) formol gel test N pk (IndMG 62 447 1926) Chopra antimony t st N pier nd Das Gupta (IndM lax 6 : 219 1934) cutaneous leish maniasi ; Shortt t L (IndJMRe 18; 13 3, 1931) tra smission by Phlebotomus grat per N pier nd Das G pta (IndMGa 69; 121 1934), kin lesions comprise r large form in 4 per cent of kala azar; Ma Le l (JTropM 37 358 1934) curette and ca stic treatm t of lupoid form Forkne nd Zia (J Exper M 63 491 1934; 61 183, 1935) parasites i nasal secretion; Lee nd Chu (ChinMJ 49 328, 1935) urea stibamine and neostibosan compared Smith nd Hobler (IndMGax 70 544 1935), dermal l, leptomeni al nd ulcerativ lesions N pier (Lancet 2:1 6 1936) plenic puncture diagnostic tech ic Istma and Wise (PhiIExper Biol 35 124 1936) formol g l test M nd T ng (Chi MJ 51 ; 449 1937) pharyngeal lesions; Sinton (IndJMRes 5 747 1936) t smission from dog t ma ; Pratt r (BMJ 1: 14, 1939) non levratly l rg painles t m l tongue Chung (ChinMJ 5 ; 501 1940) identity of L ca is nd L donov , hun nd Chang (ChinMJ 5 44 1940) Il tibl yl treatment Sco el (V l tM 1 497 1944) epi lemiology in China follow bel of Y llow Ri er disease of famine flood nd w , occurs in illages, affects males l pref rence t females 10 t 1, peak ag groups 6 10, 11 15 Most nd La letes (Med 26 321 1947), neostibosan best, 0 2 Gm IV daily for 17 d) N pk (BMJ 2 255 1930), dermal lesion follow in kala-azar circumoral rythema, small macules of hypopigmentation face neck, arms, thighs l t nd l eruption face nd ea lobes diagnosed by biopsy

TRYPANOSOMIASIS

Trypanosomes are flagellates which have a fusiform fringed body containing two stainable ma ses of chromatin one of which, large a d generally centrally located, is the nucleus a d the oth r small r and caudally located, i the blepharoplast From it arises a whip or flag lla f t ned along the bod so as to produce an u dulati g membrane the a terior en l being generally free *T gambiense* and *T rhodesiense* cause West and East African sleeping sickness respecti ely *T cruzi* causes South American Chagas disease

Symptoms.—African trypa osomes are inoculated by the bites of flies most of which are members of the genus *Glo sina* The site of inoculation the bite i scarcel distinctive prod i g nothing more tha wheal which disappears rath r promptly The region l lymph odes may exceptionally become enlarged prompti after the bite Striki g changes in the kin occur in Europea patients in the form of erythema multiforme-like lesions of polycyclic and annular type Among Negroes itchi g papules are more commonly seen. Area of hyperses itiveness are found in a high proportion of the patient affecting both the skin and deeper part ; the lea t blow or pi ching of deeper masses produces within a second or two such acute pai peculiarly d la ed a to make the subject actually cry out (Kerand l s sign) Generalized edema or true myxedema i a part of the symptom com ple and may be d e particularly in the South American disease to actual damage of the th roid gland These cutaneou phenomena occur in the primary stage of the disease when hyperpyrexia a d acute respiratory and circulatory symptoms are present. They may last for several months or ears with remission Duri g the acute form of Chagas disease t mef ction of the face may be marked, especially of one eyelid and cheek, but the edema loes not pit on pres re See Craig and Faust (Clinical Parasitology Lea & Febiger 1951 p. 182 ff)

METAZOA

Metazoans of many kinds provoke eczematous dermatitis. Among the Coelenterata the Portuguese man-of war provokes coryzal symptoms, pain in toxication and severe urticarial dermatitis by attaching on contact with the skin, its venomous nematocysts (Thomas FlaMAJ 26 83 1939) ACTH, cortisone and Chlor Trimeton promptly relieved a patient of mine

Contact with coral led to urticaria and dermatitis venenata reported Levin and Behrman (ADS 44 600 1941) and a hydroid of the genus Halecium produced similar responses (De Oreo ADS 54 637 1946) Fishermen working the Dogger Bank are subject to coral dermatitis as an occupational disease *Alcyonidium hirsutum* being the irritating animal reported Bonnevie (ActaAllerg 1 40 1948) Ulcers resulting from contact with coral seemed to be associated with malnutrition thought Philps (BMJ 1 846 1950) who recommended first a week of rest and palliation then excision

Jellyfish intoxication and dermatitis were discussed by Stuart and Slagle (USNMBull 41 497 1943) who noted similarity to black widow spider bite They gave calcium gluconate 10 cc. of 10% with prompt benefit Zieman (J 99 1713 1932) advised drying immediately after contact and dry pressure dressings. Contact with jellyfish in tropical waters causes not only redness, urticaria and burning pain at the site of contact, but spasm of respiratory

muscles, difficulty in respiration, pain in the abdominal and back muscles, cough with expectoration, profuse lacrimation, dilation of pupils, nausea dizziness, extreme restlessness and anxiety

The effects of the sting ray are quite similar (Evans BMJ 2 165 1945) Henderson (BMJ 2 300 1945) described his own experience, an unpleasant one indeed, for he almost drowned he obtained considerable relief with brandy Neubert (BMJ 2 839 1948) suffered severely for several days: the area of contact the lip underwent vesiculation and crusting Stung again a few days afterward, his reaction was much less violent suggesting the development of some degree of immunity

Zoacanthoses is a term proposed to cover those dermatoses caused by the introduction and retention of animal structures such as piercing mouth parts and bristles. Some are essentially foreign body irritants many of them are venomous rather than mechanical lesions. Immunity to metazoa may be manifested by encasement in fibrous tissue, inflammatory expulsion from the gut, antibody formation and cellular reaction and more or less specific im munologic diagnostic tests have been devised (Taliaferro AMJTropM 20 169 1940 PhysRev 20 469 1940) See Culbertson (Immunity Against Ani mal Parasites, Columbia U Press, 1942)

Urticaria and eosinophilia accompany many metazoan infections. Hel minthiasis is capable of inducing malnutrition, accompanied by xerosis as of avitaminosis A, pruritus, and pellagra

All metazoa parasitizing man are bilaterally symmetric. They fall into 4 phyla (Brumpt, 1949)

Soft skinned	PLATYHELMINTHES (Flatworms) with body with or without segmentation; celom obliterated. Digestive system if present usually lacks anus.	WORMS
	ANNELIDA (Roundworms) with body segmented celom present.	WORMS
Chitinous integument	NEMATHELMINTHES (Roundworms) with body nonsegmented no articulated limbs.	WORMS
	ARTHROPODA, segmented limbs jointed.	ARACHNIDS MYRIAPODS INSECTS

HELMINTHIC INFESTATIONS

The word helminth, as usually interpreted, now includes both parasitic and free-living species of the roundworms (**Phylum Nematoda**), the hair snakes or gordiid worms (**Phylum Nematomorpha**) the turbellarians, flukes and tapeworms (**Phylum Platyhelminthes**) and the thorny-headed worms (**Phylum Acanthocephala**) By a still more liberal interpretation it may also include the leeches, a Class group of the **Phylum Annelida** (Craig and Faust Clinical Parasitology Lea & Febiger 1951 p 293) See also Faust (Human Helminthology Lea & Febiger 1949)

NEMATHELMINTHES

Nematodes possess an intestinal tract but no proboscis, and the body cavity is not lined with epithelium. They are divided into Aphasmidia and Phasmidia, depending on their lack or possession of phasmids, which are caudal chemoreceptors.

THE PHASMIDIA contain 10 superfamilies, of which the following are of dermatologic interest Rhabditoidea (strongyloidiasis) Strongyloidea (ancylostomiasis) Oxyuroidea (enterobiasis) Ascaridoidea (ascariasis) Spiruroidea (gnathostomiasis) Filarioidea (filariasis, onchocerciasis, loasis) and Dracunculoidea (dracontiasis)

THE APHASMIDIA include the Trichinelloidea, in which the anterior part of the body is filiform, esophagus degenerate 1 testine cellular sexes hologonic, the female with single ovary; polymyarian.

APHASMID NEMATODE INFESTATION

Trichiniasis.—Trichinella contains the single species *T spiralis* of which the adult worm inhabits the small intestine and the larvae emigrate into the muscles where they become encysted They infest the human being cat rat dog pig and other animals. Cutaneous symptoms occur in a small proportion of cases (Spink and Augustine J 104 1801 1935) and include a maculopapular exanthem resembling rose spots scarlatiniform erythema and erythema multiforme Edema of the eyelids photophobia chemosis subconjunctival petechiae rose spots and urticaria are common Urticaria may be the first symptom (Musger DZtschr C8 34 1933) Splinter hemorrhages be-



Fig. 778—Trichiniasis, [illegible] showing edema of face and typical sitting [illegible] palpebral fissures (Dr John W Perkins)
Fig. 779—Splinter hemorrhages under fingernail in trichinosis. (Dr L H Briggs)
Fig. 780—Trichinella larva in sediment of digested human muscle X18. (McNaught AmJTropM 19 181 1939)
Fig. 781—*Encysted trichinella in human muscle cells* (Dr J B McNaught)

neath the nails are petechiae due to larval migrations seen in some 60% of active cases (McNaught AmJTropM 19 181 1939) they were present in 10% of the cases of Semple et al (BMJ 1 1002, 1954) Scarlatiniform eruptions were seen in 2 of 6 cases by Millett (BullUMdMSch 28 163 1944)

The administration of streptomycin in an acute case was followed by immediate fall of the temperature to normal (Tate and Wheeler TransMS 51 11 1950) ACTH effected dramatic relief of fever dyspnea aching and other symptoms in 8 patients of Buylla (abs J 153 690 1953)

The Bachman Skin Test using as antigen a 1 10 000 dilution of saline extract of larvae is of interest. It does not become positive before the second week after onset of symptoms (McCoy et al. JImmun 24 1 1933) and is an

immediate wheal type of reaction when positive (Spink NEngJM 216 5 1937) Perhaps 10% of reactions are false positives, for reactivity once established persists for years (Warren et al. AnnIntM 13 2141 1940)

See Bachman (JPreventM 2 35, 169 513 1928) intradermal test Fritlander (AmJMed Sci 188: 121, 1934) skin test is unreliable in diagnosis Drake et al. (J 105 1340, 1935) Maine epidemic with classic kid symptoms Hall (PublHRpts 52: 539 1937) atypical cases, precipitin test becomes positive later than skin test, organisms found in about 13% of cadavers.

PHASMID NEMATODE INFESTATION

Strongyloidiasis.—Phasmid nematodes of the superfamily Rhabditoidea include the species *Strongyloides stercoralis*. The free-living generation lives in the soil, a roundworm roughly 1 mm. long and 50 μ in diameter The fertilized female discharges embryonated eggs which hatch within a few hours, and rhabditoid larvae emerge feed moult and soon grow into free-living adults. These may metamorphose in unfavorable conditions into filariform larvae resembling those of the hookworm and as such are infective for man, capable of remaining alive in the soil for many weeks On contact with the skin or mucous membranes, they penetrate, producing a petechia and intense pruritus at each site followed by edema and perhaps by secondary infection. Some reach blood vessels and are carried to the lungs, where they perforate the endothelium, enter the alveoli, induce a pneumonitis simulating bronchopneumonia, pass up the respiratory tree, and are swallowed. Reaching the intestine they lodge in the villi and crypts, mature and deposit eggs.

Studying transmission of infection experimentally, Tomita (abs J 117: 11 4, 1941) applied sw be wet with suspensions of *S. papillosus* and *S. fülleborni* to the skin, finding within 4 hours redness, warmth tingling sensations and sometimes vesicular lesions. *S. papillosus* evoked considerably more severe reactions locally but the other parasite induced systemic reactions including urticaria, gastrointestinal upset and sometimes fever

Diagnosis requires the identification of larvae in the feces. A skin test was devised by Fülleborn (ArchSchiffsTropHyg 30: 731, 732, 1926)

Gentian violet enteric-coated tablets of 1 grain size 3 times a day for a fortnight usually succeeds. See Simpson (J 11 828 1939) Craig and Faust (1951)

Ancylostomiasis.—Phasmid nematodes of the superfamily Strongyloidea include the Ancylostomatidae the human hookworms, which are characterized by their possession of oral cutting organs, toothlike processes in the genus Ancylostoma, semilunar plates in Necator Larvae of these worms may penetrate the skin, causing more or less severe irritation and dermatitis.

Ancylostoma duodenale, common in Europe and the Mediterranean region, is a cylindric worm, 10 to 18 mm. long which lives in the small intestine. The eggs, laid in the intestine of man, are passed with the feces, and become larvae. After development, these larvae can penetrate the skin, circulate in the blood and enter the lungs, whence, via trachea and esophagus, they reach the intestine to undergo evolution into adult form. *Necator americanus* is a similar parasite common in America. Penetration of the skin is not done through hair follicles. The lesions in sections show dense eosinophilic infiltration.

Itching, redness, and small pustules result from the percutaneous migration which requires only a few minutes. Bacteria may be introduced into the tissues along with the larvae. Ground itch, miners itch, water itch and mazamorro are lay names applied to the dermatosis. Cutaneous ancylostomiasis usually begins between the toes and extends over the foot. Itchy plaques and erythematous macules may be succeeded by vesicles, pustules and ulceration.

Percutaneous infection with larvae obtained from stools has been used in the treatment of polycythemia (Brumpt and Gajar: IndMGaz 83: 166, 1948)

Catarrhal bronchitis may symptomatically demarcate the passage of the larvae through the lungs. Eosinophilic pneumonopathy Loeffler's syndrome occurring in conjunction with cutaneous helminthiasis, represents an allergic phenomenon. Wright and Gold (J 128 1082, 1945) observed in 9 of 15 cases of creeping ancylostomiasis transient migratory pulmonary infiltration with little or no sign or symptom of systemic disease except eosinophilia of the blood (Wright and Gold: AIntM 78: 303, 1946; Kalmon: Radiol 63: 223 1954) *A. braziliense* was found in the sputum of a patient of Muhleisen (AnnIntM 38 595, 1953)

CREEPING ANCYLOSTOMIASIS.—*Ancylostoma braziliense* of which the dog is the natural host, causes, in its larval state a type of creeping eruption. The disease is common along the coast of the southern part of the United States. Infested cats or dogs inoculate the soil with their feces, and in moist, shady sand or earth mature filiform larvae invade the skin of human beings when opportunity offers. A reddish, itchy papule marks the site of entry and within 2 or 3 days a sinuous tunnel in the epidermis has been produced. The lesion is first erythematous it becomes elevated and vesicular The larva

moves several millimeters or even centimeters per day The portion of the tunnel first made and so first abandoned tends to heal Itching is severe The number of lesions depends on the number of infesting larvae tunnels may be solitary or numerous Exposed portions of the body are the sites of predilection. A larva may persist with its wanderings for several weeks or even months (Dove AmJHyg 15 664 1932)

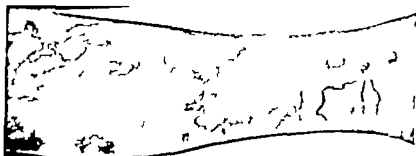


Fig. 782.—Creeping eruption due to Ancylostoma braziliense (Dr O. G Costa.)



Fig. 783—Creeping ancylostomiasis in child's boy back. (Dr Grover Wende)

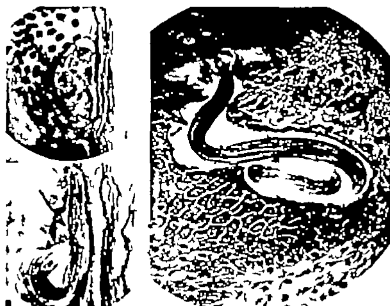


Fig 784—*Ancylostoma braziliense* larvae shown by histologic sections in human epidermis. (Kirby-Smith, White and Dove ADS 13 137 1926)

The larva, located at the terminus of its tunnel may be frozen in situ with the ethyl chloride spray this treatment is usually effectual This is the only treatment which has stood the test of time according to Sompayrac (SouthMJ 47 792, 1954) Halley (SouthMJ 39 371 1946) stated that a grated raw onion poultice applied thick, overnight for 3 to 7 nights, will do the job

In seeking larvae in the skin, where they can be seen with a hand lens, one cleanses the skin at the suspected site with alcohol and applies cedar-wood oil to clear it. The end of the burrow is carefully examined, and the larva appears as a white spheric mass (Bayley: TransRoySocTropM 34: 399 1941) The site may then be anesthetized with procaine and the larva destroyed with the actual cautery or with the electric needle (Farrington: JID 14: 395 1950) Stibanose a pentavalent antimonyl, is said to be less toxic than Fuadin, and by stopping the movement of the larva makes easier its localization and destruction by freezing (Wilson: SouthMJ 45: 177 1952)

Cure might be obtained by intramuscular injections of Fuadin, 6 3% solution 2 cc daily for 5 doses, perhaps repeated after a week's rest according to Smith (J 123 694 1943) Wilson (FlaMAJ 30 425 1944) and Hitch (ADS 55 664, 1947) confirmed this, but Blank (J 123 989 1943) and Dolce and Franklin (ADS 52 174 1945) reported disappointing results. Systemic therapy was judged ineffectual by Loewenthal (AustralJD 2 173 1954)

Hetrazan (diethylcarbamazine) given orally in a dose of 2 mg./kg t.i.d. for 7 days, cured 17 of 19 cases of Van de Frye (JID 12 69 1949) and was almost as effective in the cases of Horton (USAFMJ 1 668 1950) its side effects were few and mild. A dose of some 9 to 10 mg./kg given in syrup t.i.d. for 5 or 6 days was highly recommended by Kelley (FlaMAJ 40 242, 1953)

CREEPING ERUPTION may be due to larvae other than those of *A braziliense* and is representative of frustration of the normal complete penetration and pursuit of its life cycle by a parasite attacking an unsatisfactory host (Caplan: BMJ 1: 433 1950) *Bunostomum phlebotomum* the hookworm of cattle (JParasit 39: 343 1953) can cause creeping eruption on the hands of exposed human beings (Mayhew: ProcSocExpB 66: 12, 1947): small, inflamed papules appear enlarge for 2 or 3 days and are followed by narrow linear slowly extending tortuous, vesicular lesions which itch intensely but clear spontaneously in a fortnight.

Creeping eruption may be due to several kinds of parasites see Gnathostomiasis, Schistosomiasis, Tetranychus infestation and Myiasis.

Ascariasis.—Phasmid nematodes of the superfamily Ascaroidea are fairly large stout forms possessing a mouth with 3 conspicuous lips but without a buccal capsule. *Ascaris lumbricoides* is a round white intestinal parasite ranging up to 10 inches long Infestation is a possible cause of urticaria or prurigo (Stauffer Dermatologica 105 203 1952) and erythema nodosum has appeared in heavily infested children. Cutaneous allergy develops (Borlin Dermatologica 92 187 1946) The life history of the parasite was discussed by Moore (SouthMJ 47 825 1954)

Oxyuriasis.—Phasmid nematodes of the superfamily Oxyuroidea are small forms more or less pin-shaped, with buccal capsule and cuticular esophageal lining well developed.

Enterobius (Oxyuris) vermicularis adults are white worms 2 to 13 mm. in length and 0 1 to 0.5 mm. in diameter the male being about one-third the size of the female. Called pinworms, these inhabit the human ileum, cecum appendix and ascending colon, their heads attached to the mucous membrane of the intestine The female with full uterus migrates toward the anus, and thousands of eggs are laid in the dejecta and rectal mucus. Ova, when swallowed, hatch in the duodenum, and the larvae moult and lodge in the distal gut.

Pruritus ani results from infestation. It is a symptom of remarkable periodicity appearing always in the evening at bed hour probably because of the warmth and quiet which encourage great activity on the part of the worms near the anus. Erythema of the anal margin is seen, with many reddish points from the bites of the worms; there is considerable thick and sometimes blood tinged mucus, in which ova are to be found. Vulvar and vaginal involvement occurs. Otitis externa so caused was observed by Hand and Criswell (ADS 59 249 1949) and was cured by the instillation of benzyl benzoate.

In diagnosis an anal swab is made of Scotch tape wrapped sticky side out about the closed end of a test tube. The sticky surface is rocked against the anus, and the tape is then pasted on a slide and examined for adhering ova (Jacobs JPed 21 497 1942; v.Hofe: J 125 27 1944)

Thymol is a useful vermifuge A dose of 4 grams may be given an adult 1 or 2 to a child dividing the dose into 0.5 Gm parts, giving one part each hour and following the last dose with a saline purge Hexylresorcinol crystoids, 1 Gm. for adults and 0 6 to 0.8 Gm. for children are recommended. The dose is swallowed without chewing in the morning on an empty stomach. Gentian violet also is useful internally 1 grain enteric-coated t.i.d. for 10 days being an adult dose (Wright and Brady AmJMedSci 198 367 1939 J 114 861 1940) Benadryl Emplets, 50 mg daily for 10 days for little children and thrice this dose for patients over 12 years old were reported curative by Siung (BMJ 1 822, 1950) Piperazine hexahydrate is nontoxic safe and effective (Bunibalo et al JPediat 44: 386 1954) Terramycin is the drug of choice among pediatricians currently (Wells et al. Antibiot&Chemother 1 299 1951)

Gnathostomiasis and Related Worm Infestations.—SPIRUROIDEA, a superfamily of phasmid nematodes contains several species of dermatologic interest. *Gongylonema pulchrum* has been reported in the southern ... United States. It eggs are ingested by beetles or cockroaches within which they hatch and burrow and subsequently reach the mucosa of the human mouth throat or esophagus, where they tunnel and migrate Mechanical removal of the threadworms can be accomplished.

Swelling and hyperemia of a girl's lip due to thi parasite was observed by Stiles and Baker (J 91: 1901 1928) and they reviewed 5 other cases. A case occurring in South Carolina was reported on by Young and Hayne (J 151: 140 1953) The parasit ca ing a forearm nodule seen by Forbes (Lancet 1: 651 1919) was not specifically identified. Migrating and itching swellings of the skin associated with high eosinophilia and positive cutaneous reacti ity to an antigen from *Di ofilaria immitis* were seen in Palestin (J 121: ..30 1940) and may have been f this nature for threadworm produce migratory nodules.

Gnathostoma spinigerum para itizes the tiger and other host i the Far East. Eggs in feces hatch out motile larvae which enter a *Cyclops* and later a second intermediary host. In the human being immature worm usually penetrate only superficially prod cing sta t onary or migratory lesion which are abscesses or firm nodules with abscessed centers. G athostomia causing creeping eruption, acute edema, abscesses and nodules can be prevented by cooking fi h sufficiently to kill the vector (Kitamura: ADS 66: ..6, 1952)

Thelazia call pa da i a parasite of the conjunctiva of dog rabbit and man, occurring n China, Burma and India. Other species exist which also evince predilection f r the ocular region. Arthropodan intermediary hosts are involved, and the adult worms, perhaps longe than 1 cm. and creamy white coil in the conjunctival sac and migrate so as to prod ce severe pain lacrimation and irritation, which may provoke scarring of the cornea. They may be removed mechanically *T. cal forniensis* wa the parasite fou d in the conjunct va of the patient of Hosford et al. (AOphth ..: 1165 1942)

Filariasis.—Phasmid nematodes of the superfamily Filarioidea are filiform worms with a simple mouth almost circular surrounded by papillae lacking lips and with buccal cavity at most rudimentary The adult lives in the tissues or body cavity of a vertebrate host

Eggs re partially embryonated before birth, and at about the time of oviposition th embryos uncoil as delicate snakelike microfilariae These circulate in the blood or move in the cutaneous ti sues and are ingested by blood-sucking arthropods. Migrating from the digestive tract of the arthropod vector they undergo m tamorphosis, and mat re larvae migrate into and down th hemocelic cavity in the labium so as to reach the kin of the vertebrate host upon which the vector next feeds.

Wuchereria bancrofti (Filaria sa guinis hominis) is a creamy slender smooth skinned worm th adults of which, several centimeters in length, live in the human lymphatic system. The microfilariae are 100 to 400 times a numerous in the blood at night as during the day although those of the South Pacific lack such periodicity They measure 150 to 320 μ by about 10 μ in diameter Their evolution continues in mosquitoes and they introduce themselves actively through the skin of the human being when the mosquito attacks. Several vectors in add tion to the usual *Culex fatigans* have been determined.

Filariasis occurs in Hungary a d T rkey th Far East Burma, Indi I do China, and vicinity the Dutch East Indies, Philippines, northern Australia and Micronesia, North Africa and northern South America. The hyperendemic areas of yaws and Bancroft's filariasis are notably coextensive (Craig and Faust)

W malayi s a similar worm reported from th Dutch East Indies in association with elephantiasis usually of the uppe extremity It is distinct from *W bancrofti*, which it resembles, but its m rofilariae show two distinct nuclei in the tip of the tail (Craig and F ust 1951)

SYMPTOMS.—Early clinical manifestations of filariasis were clarified by Saphir (J 128 1142. 1945) comprising a well-defined clinical picture Saphir's patients were men exposed in a heavily infected area Within 3 to 6 months

Fig. 785.—Filarial elephantiasis. (Dr Harry M Robinson, Jr.)
Fig. 786.—Hydrocele due to W bancrofti infestation. (Dr Harry M. Robinson, Jr.)

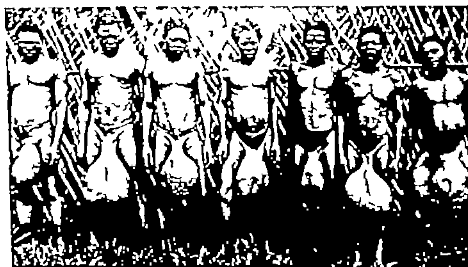


Fig 787 —Filarial elephantiasis, 6 cases. Patient at left has hernia. (Dr L. F J ...gard)

insidiously progressive and intermittent complaints developed with feelings of numbness of an extremity particularly at night followed by aching abetted by exertion and the discovery of axillary or inguinal lymphadenopathy. Periodically recurring pains in axillary, arm, groin, thigh and scrotal regions ensued and nocturnal orchiodynia was commonly experienced. By this time examination would reveal lymphatic and genital findings: multiple slightly tender firm discrete movable lymph nodes of axillary, inguinal and femoral regions regularly and other sites occasionally; funiculitis usually left-sided and occasionally varicocele, hydrocele and epididymitis. Funicular involvement was palpable as a peculiarly nodular tender thickening. Microfilariae could not be demonstrated and diagnostic skin tests were without value. If the patient were removed from the endemic area nothing further developed. Anxiety especially concerned with potential harm to genital function was usual, but such fear was groundless.

Progress of disease beyond the early stages is characterized by lymphangiitis associated with a red streak and perhaps palpable enlargement of the vessel. Dull red, tense, edematous, painful swellings occur in arms or legs. Urticaria and eosinophilia sometimes are met but not always. Swellings develop rapidly, regress and recur. Fever and malaise may accompany these exacerbations. No case of elephantiasis developed in an American soldier and the hazard to the public occasioned by returning military personnel apparently is negligible.

Late stages are characterized by chronic hyperplastic changes in the skin and subcutaneous tissues, which are due to lymph obstruction and inflammation and which may result in enormous increase in size of the affected part known as elephantiasis. Chylous effusions in the chest and abdomen are occasional late manifestations.

DIAGNOSIS is justified in early stages in endemic areas on clinical grounds alone. Exacerbation precipitated by exercise are suggestive. Proof of infection requires demonstration of microfilariae. In the blood they are curiously much more numerous at night than in the daytime (O'Connor: JTropM 40: [illegible], 1937). The mosquito abstracts more of them from a man than can be found in an equal quantity of blood obtained by pin prick (Manson: Filaria Sanguinis Hominis, Lewis 1883; O'Connor and Beatty: JTropM 40: 101, 1937). This periodicity may be concerned with diurnal changes of blood oxygenation (McFadzean: BMJ 1: 1106, [illegible]). Microfilariae may be found in lymph node or hydrocele fluid, or a calcified worm may show up roentgenographically.

The skin test using *Dirofilaria immitis* antigen is of dubious value and the antigenicity of various worms is not greatly different as judged by such test (Lippelt and Mohr: KlWchnschr 17: 1694, 1938).

Histologic changes are those of chronic inflammation, nonspecific unless identifiable worm substance can be found (Michael: USNMBull 45: 225, 1945; Rifkin and Thompson: APath 40: 220, 1945).

TREATMENT during acute attacks should consist of rest and compresses and elevation if swelling and pain indicate their desirability. X-ray therapy and surgery are not advisable then, but elephantiasis may be attacked surgically. Neostibosan in increasing dosage reaching 300 mg., on alternate days, may be given for a month or more; this by influencing adult worms, diminishes the production of embryos (Culbertson et al. AmJTropM [illegible] 130 534 1946). Anthiomaline may be useful (Brown: J 125 952, 1944). Encouraging results with Hetrazan (1-diethylcarbamyl-4-methyl piperazine dihydrogen citrate) were reported by Stevenson et al (J 135 708, 1947) in doses by mouth of 0.5 to 2 mg./kg. t.i.d. for from 3 to 22 days. The drug rapidly eliminates microfilariae from the blood but not from hydroceles and it is not toxic to them in vitro (Hawking and Laurie: Lancet 2: 146, 1949). Its usefulness was first attested by Hewitt (J 136: 708, 1947) but it caused enough side effects in a fourth of the Gambian patients treated by McGregor et al. (BMJ 2: 908, 1952) to earn a bad lay reputation. Avoidance of infected villages, mosquito control, protective clothing and bed nets and insecticidal efforts are indicated when one must stay where the disease occurs (WDTBM no. 142, 1945).



Fig. 788.—Nonfilarial elephantiasis of genitalia, associated with bilateral bubo, rectal stricture and perineal sinuses (lymphopathia venerea[4]) (Dr T G Orr)

Fig 789—Filarial elephantiasis of scrotum in a native of the Belgian Congo. (Dr E. R. Kellersberger)



Fig 790—Elephantiasis of leg. (Dr W M. Pickard)

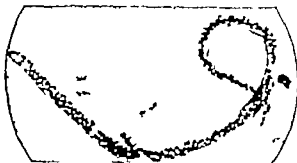


Fig 791.—Wuchereria bancrofti, microfilaria which has emerged from sheath. (Army Medical Museum, from Meakins Practice of Medicine, Mosby Co.)

See Kellersberger (J 82: 1197 1924) surgical removal of 85 lb. of scrotal tissue; Earl (Lancet 2 667 1941), suppression with sulfapyridine; Grace (J 123 462, 1943), relatively little benefit from sulfonamide; Wartman (AmJTropM 24 299 1944) in W Pacific cases, diagnosis; Thompson et al. (J 129 1074 1945) early infections, clinical features; Hodge et al (AmJMedSci 210: 207 1945) early filariasis; Coggeshall (J 131, 8, 1946) lymph tissue appears but not seen in soldiers stationed in Samoan Islands; Welch et al (Ibid 105 486 1947) cyanine compounds in treatment; McFadzean and Hawking (BMJ 1 936, 1951) arsenamide 125 mg. I V daily ×10 effective, seldom fatal.

Sporadic Elephantiasis may follow recurrent cellulitis due to bacteria or dermatophytid or it may be due to malformation or to other causes of lymphatic obstruction. Luke (SGO 73: 4 , 1941) listed chronic enlargement of the leg under 6 headings: congenital hypertrophy lymphatic stasis congenital or acquired developmental venous retardation, mixed venous and lymphatic partial obstruction arteriovenous fistulas and miscellaneous. Nonfilarial elephantiasis may be due to recurrent erysipelas (q.v.) carcinomatous obstruction of lymphatics (see cancer metastatic) surgical removal of lymphatics in the treatment of cancer lymphangioma or hemangioma (q.v.) form of von Recklinghausen's disease (q.v.) chromoblastomycosis (q.v.) and other agencies.

See Shattuck (BostonM&SJ 163: 18, 1910) etiology; Stevens (J 100 1754 1933) recurrent erysipelas; New and Kirch (J 100 1230 1933) facial palsy; Homans et al (AnnSurg 100 812, 1934) animal experiments relation to high protein concentration in tissue fluid; Allen and Ghormley (AnnIntM 9 516, 1935) classification of 300 Mayo cases in of lower extremities; Montgomery (ArchIntM 57: 1148, 1936), secondary to cancer of ankle; Hill (BMJ 2 673, 1936) following trauma; Veal (J 108 1236, 1937) vasographic studies of surgical obstruction cases; Cooperstock (AmJDisChild 57 309 1939) congenital; Homans (ArchSurg 40: 732, 1940), varieties of leg cases; Netherton and Curtis (AJDS 41 11 1940) diffuse hypertrophic syphiloma and lymphopathia venerea; Macey (PMSMC 15: 49 1940) nevoid; Allen and Hines (PMSMC 15 164 1940) orthostatic in fat girls; Hovnanian (ConnMJ 13 44, 1949) unusual scrotal case surgically relieved; Blocker (Plast&ReconstrSurg 4 407 1949) treatment; DeTakats and Evoy (Angiol 1 73, 1950) 150 cases of lymphedema treated with elevation, compression, mercurial diuresis heparinization, interruption of sympathetic innervation, x-ray excision; Pratt (J 147 11 1 1951 151: 888 1953) surgical correction.

Pseudoleprosy of Robles was reviewed by Mazzoth (MedMex 21: 103, 1941) who described 6 cases of chronic solid edema of the feet. The disease begins with erythematous macules on the lower third of the leg and persists for several years with non-suppurative inguinal adenitis. Progress takes place with febrile attacks of a few days duration, with enlargement of the affected parts. These attacks diminish in frequency after a few years. The onset is usually at an age between 6 and 20 years. No radiographic alterations are found and no parasites have been discovered although all varieties have been sought. The disease is unresponsive to therapy.

Onchocerciasis.—Filarial worms of the genus Onchocerca inhabit connective tissues and blood vessels of mammals; in man they tend to accumulate beneath the epidermis. Black gnats (Simulium) are the usual vectors.

O volvulus has a transparent opaline body. The mouth is smooth. The male is 30 by 0.13 mm., with rolled up tail; the female reaches a size of 50 by 0.36 mm., and is viviparous. Both sexes are found in the subcutaneous tumors, which range from pea to pigeon egg size and are located in scattered places; the popliteal, lumbar, intercostal, axillary, epitrochlear and nuchal regions. The tumors are nematodic and contain adult and numerous embryo worms in canals in fibrotic tissue. They are generally readily enucleated, and they never occur in deep organs. The evolution is slow, the worm living many years. The tumors never ulcerate. Despite frequent exposure to infected bites, the natives in endemic zones may have only 1 or 2 verminous tumors; some sort of immunity may develop.

The embryos are some 300 by 6 or 8 μ in size; they have no sheath. They migrate in the connective tissue. They are much more numerous in the vicinity of the bite of a vector than elsewhere in the skin.

Symptoms.—In Mexico especially Chiapas and Oaxaca, and Guatemala, infestation is common. In American cases, tumors containing *O volvulus (O caecutiens)* are almost always located on the head. Microfilariae in their migrations are especially liable to enter the cornea iris and conjunctivae so causing scarring and eventually blindness. Cutaneous lesions may resemble erysipelas in the acute phase. Chronic infection results in edema, eczema with hyperpigmentation and especially swelling of the ears. The skin nodules *range from 0.8 to 30 or 40 mm. in diameter* and are hard and red but not painful. In American cases the number is usually less than 8 and they are generally on the head, while in African cases the number ranges from 25 to 100 and the trunk and limbs are the sites of predilection. Ocular lesions were found in about 60% of persons with fewer than 5 nodules but in almost 80% of patients with more than 5 nodules reported Solanes et al. (AmJOphth 32 1207 1949). The nodules contain turbid liquid rife with microfilariae swimming about a core of adult parasites enmeshed in atrophic connective tissue



Fig. 792.—Onchocerciasis. Verminous tumors f typical character and location in the Central American disease. (Courtesy of Dr Richard P Strong, Dr J H. Sandground, Dr J C. Bequaert, and Dr M. M. Ochoa, and the Harvard University Press, 1934.)

Fig. 793.—Onchocerciasis. Pigmented plaques of the face. The dermis in these lesions manifests cellular proliferation and infiltration, and it contains microfilariae. (Dr R P Strong.)

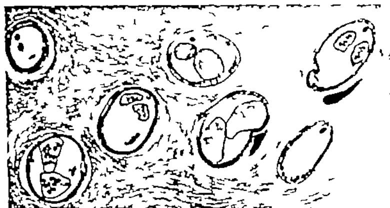


Fig. 794.—O volvulus adult worms in erminous tumor of scalp. (Dr Ldw A Gall.)

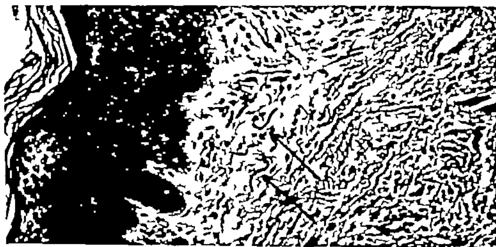


Fig. 795.—Onchocercal dermatitis, erythematous, squamous and papula showing microfilaria in the dermis. (Goldman ADS 49 335, 1944)

PREVENTION consists in staying away from infested regions. If one lives there one must destroy flies, avoid their bites, and excise verminous tumors as promptly as they appear

TREATMENT — A strong solution of Apothesine injected into the verminous tumor kills the parasites renders excision unnecessary, and relieves the symptoms of craw-craw (Stixrud 1938) Roberto (MMéxic 24 265 1944) found wiggling microfilariae in fresh split skin biopsies immersed in saline Hetrazan and Germanin, effective drugs in W bancrofti infection apparently kill the organisms in O volvulus infection but here their administration is followed by intensification of symptoms analogous to the Herxheimer reaction with pruritus, urticaria fever and lymphadenopathy presumably due to rapid killing of the organisms, and the doses must be small and relatively infrequent (Hawking and Laurie Lancet 2 146 1949 Hawking: BMJ 1 992, 1952) Germanin appears to be superior Hetrazan treatment was tried by Ikejiani (W AfricaMJ 3: 135 1954) in whose experience the value of *Dirofilaria immitis* antigen appeared to be doubtful Hetrazan did not visibly influence the worms as observed in nodules excised after it was given It did, however cause itching in all patients during the first day, and occasionally rashes, fever aching leukocytosis and lymphadenopathy Skin lesions began to disappear after the fourth day and were gone within 2 months, only to relapse later The drug evidently affected microfilariae but not adult worms.

FILARIAL ITCH is a manifestation of onchocercal infestation. This is one variety of craw-craw a nonspecific native name The dermatosis is not pathognomonic It occurs in Central Africa Ceylon and China and probably elsewhere Papulopustules and plaques which may crust ulcerate and leave scars are typical The buttocks and flanks the outer side of the thighs, the elbows, forearms and rarely the neck are involved the face genitals and interdigital volar and mucosal surfaces are usually free Repeated attacks occur and the eruption is therefore polymorphous. Urticaria may accompany the attacks. The dermatosis does not of course respond to antiscabietic treatment It resembles dermatitis herpetiformis.

See Strong (NEngJM 204 916, 1931) Strong et al (Onchocerciasis, Harvard Univ Press, 1934, p 234) monograph Bryant (TransRoySocTropM 28 523, 1935) in Anglo Egyptian Sudan Herrejon (quoted J 106 579, 1936) blindness in 30% of population in some places Semadeni (SchweizMW hn 70 75, 1940) slit lamp demonstration in eyes Harris (TransRoySocTropM 34 223 1940) nauk [illegible] Kenya, ichthyosiform and lephantiasic changes Goldman (ADH 50 388, 1944), review and illustration Goldman and Ortiz (ADS 53 9 1946) cutaneous features Ophthalmologic Assn of Guatemala, Unal of S Carlos (Onchocercosis, Enfermedad de Robles 1947 p. 287) Robles disease ; Nwokolo (TransRoySocTropM 43 493, 1950) Nigerian cases, none of [illegible] eyes, Craig and Faust (Clinical Parasitology Lea & Febiger, 1951 p. 4 1) de H [illegible] (BMJ [illegible] 14 1954), solitary worm found in deep groin paratyphoid [illegible] Kershaw et al, (BMJ 2 724 1954) studies of O [illegible] also microfilarial concentration and distribution in the skin, showing patterns related to distribution and severity of skin and eye lesions, with high concentration, unexplained, in lower leg and trunk region of persons infected with moderate intensity

Loasis (Calabar Swellings).—*Loa loa* has a transparent opaline body and a smooth, thick skin dotted with many small bosselation The males are some 30 by 0.33 mm. (3 times the size of *W bancrofti*) and the ovoviviparous females are some 63 by 0.4 mm. They inhabit the subcutaneous tissue and move about constantly so that little tissue reaction is present Embryos are freed into the cellular tissues and enter the lymph and blood They are some 250 to 300 by 6 to 8 μ in size They are typically found in the blood in the morning most numerous there shortly after noon, and they disappear in the evening The mango fly is a vector

In equatorial Africa many natives harbor the parasite in the blood. The adult worm in its migration produces egg-size painless warm swellings resembling angioneurotic edema. Where the skin is thin the outline of the worm itself may be visible They have been known to traverse the conjunctiva Itching eosinophilia and sometimes malaise and urticaria accompany the direct manifestations. Cases have been described by Kimberlin (J 81 1685 1923) Low (JTropM 37 359 1934) Charpy (BullsocfrançD 46: 180, 1939) and others. Adult worms have been surgically removed from the back, axilla, groin, breast penis, scalp eyelids and even the bulbus oculi (Craig and Faust 1951) Cure is effected by such surgical removal which requires both speed and skill and is easiest when the worm is migrating across the bridge of the nose or through the corneal conjunctiva.

Antimony and Mapharsen are not effective but departure from endemic areas is followed by eventual relief (Guy et al.: ADS 47 763, 1943) Hetrazan was used with good results, although it caused temporary malaise (compare Onchocerciasis) in 3 cases affecting missionaries observed by Ten Berg (abs YBD 1952 p. 74)

Dirofilaria conjunctivae and other filarial worms of genera different from *Loa loa* are sometimes found. *D. conjunctivae* measures in its adult form from 5 to 10 cm. in length and 0.5 mm. in diameter; it produces encysted subcutaneous nodules of the eye and other regions, and infestation is cured by its mechanical removal (Craig and Faust 1951)

Dracontiasis.—*Dracunculus medinensis*, the Guinea worm produces a remarkable infestation observed about the west coast of Africa, upper Egypt, Asia Persia and India. The female is from 30 to 100 cm. in length and 1.0 to 1.7 mm. in diameter; the male rarely discovered, is to 4 cm. long The worm lives in the subcutaneous tissues. The female develops, migrates and appears in the skin several months after one ingests with the drinking water certain crustaceans, Cyclops, infested with the larvae.

Adult worms develop within the host, and the viviparous female makes her appearance after several months, laden with larvae at the bottom of a pea-sized, indurated, itchy lesion, the site of which is frequently the foot or leg and through which larvae are extruded; or she may form a soft spongy cordlike mass under the epidermis. The parasites are usually solitary but may be multiple The condition is relatively benign. Urticarial and asthmatic attacks and gastrointestinal upsets may complicate the infestation, often just preceding the development of the local skin lesion (Fairley and Liston: IndJM Res 11: 915; Lc 92, 247 1924; Okojie: BMJ 1: 397 1954)



Fig. 190.—*Dracunculus medinensis* being extracted from foot. Five more worms subsequently issued from this Uganda native. (Dr A. L. Ribeiro BMJ 2 1310 1952.)

Emily injected 1:1,000 bichloride of mercury into the worm or the tumor it produced and after 24 hours the parasite could usually be extracted without trouble. The natives generally pull the worm out of its hole an inch or two and wrap it on a stick of wood. Each day some 3 or 4 centimeters of worm can be rolled up, and with good luck a cure may be attained in a fortnight. Rupture of the worm during its extraction must carefully be avoided. Slaked lime 1 1,000 in the supply of drinking water repeated at intervals of 14 days or so, kills the Cyclops. Boiling and filtering the water before drinking it are effective prophylactic measures.

See Chitwood (J 100 802, 1932) 4 cases in USA Rao (IndianMGaz 24 533, 1930) release of larvae from Cyclops by HCl Moorthy and Sweet (IndMGa 71 565, 1936) biologic control, using fish that eat Cyclops Perry (BMJ 2 1107, 1948) worm found in hernial sac in African youth, Katzenellenbogen (quoted J 144 1391, 1950) 40 cases from Yemen, fever at onset, cellulitis and blisters, worms seen extruding from lesions of feet, legs, buttocks, mammae, palms, penis Katzenellenbogen (Dermatologica 108 129 1954) previously unknown in Israel, 68 cases of *Dracunculus medinensis* infestation found among 48,000 Jews who emigrated from the Bulk area of Yemen.

Platyhelminthes
TREMATODE INFESTATIONS

The phylum Platyhelminthes contains 4 classes, of which the Trematodes and Cestoidea include the human pathogens.

Trematodes are exclusively parasitic organisms, the integument of the definitive stage nonciliated, suckers usually present, circulatory system lacking digestive canal present except in sporocyst generation of the subclass Digenea. This subclass contains the human pathogens. Most of the digenean species are endoparasitic, attaching by suckers, 1 of them perioral; development is complicated, involving 2 or more generations and an alternation of hosts. The host harboring the intermediate stages is a mollusc.

Prosostomata is the order inclusive of all trematodes affecting human beings and contains the flukes and schistosomes. See Craig and Faust (Clinical Parasitology Lea & Febiger 1951 pp. 445 500); Dawes (The Trematoda, Macmillan 1946)

Fluke Infestation.—In *Fasciola hepatica* an illustrative trematode the egg becomes a miracidium a free infusoriumlike embryo. This, in the intermediary host becomes a *sporocyst* which buds internally. Spores are freed and become encysted and in the liver of the definitive host give rise to the adult which produces eggs. Cutaneous nodules generally located on the trunk occur rarely as rice-grain sized sacs containing 1 to 3 worms in a slimy jelly provocative of itching during the first few weeks of subcutaneous existence later becoming firm (Stiles JCutDis 26: 34 1908) Several species of worms cause similar tumors Diagnosis can be made only after removal.

Schistosomiasis.—Schistosomatoidea is a superfamily of the order Prosostomata of the digenetic trematodes. The definitive stage is monecious or diecious, living in the portal blood streams of vertebrates. Cercariae enter the definitive host through the skin. *S haematobium* causes bilharziasis of the bladder *S mansoni* causes intestinal and splenomegalic involvement *S japonicum* causes intestinal and hepatic bilharziasis.

S haematobium cercariae penetrate within 10 minutes when the skin is exposed to polluted water losing their bifid tails at the surface and entering the veins, where in about 2 months they become adults migrate to the bladder and produce disease there During the period of invasion, urticaria may occur along with the usual toxic fever sweats and malaise Fibrous nodules sometimes appear especially in the perineal and bathing trunk areas. Hard at first they gradually enlarge soften, ultimately burst through the skin, discharging thick, dirty caseous material The sores generally persist as fistulas communicating with a deeper organ or mucous surface simulating tuberculosis (Black BMJ 2 4 3 1945) *S mansoni* cercariae penetrate the skin with the provocation of temporary severe pruritus and small papules, which appear within 6 to 8 hours afterward Urticaria and purpura may occur (Hauser NOrlM&J 92 265 1939) Creeping eruption progressing 2 inches per hour along with crusts, urticaria fever painful liver and white cell count of 64 000, 96% eosinophils, was reported by Wright and Roberts (EAfrMJ 21 282, 1944) *S japonicum* infection resembles *S mansoni*. Urticaria accompanied by fever may develop as early as the fifth day after exposure and about the end of the fourth week intense urticaria subcutaneous edema and large wheals affecting both skin and mucosae are usual followed by toxic diarrhea (Craig and Faust 1951 p 464ff Faust et al AmJTropM 26 87 1946) The patient of Fishbon (AmJTropM 26 319 1946) 1 week after exposure had angioneurotic edema of the face chills fever and cough Pruritic papules appeared on the chest and became shotty grouped or coalescent. Some developed pustulation with ova in the pus. The lesions underwent fibrosis when Fuadin was given after ova appeared in the stools.

Skin Test —An antigen may be prepared from infested snail livers, and reactivity to it indicates that the subject harbors living parasites (Fairley in Byam and Archibald Practice of Medicine in the Tropics, Oxford Univ Press, 1922 vol 3 p 1712) The immediate urticarial reaction was described by Hoff (J 107 137 1936) who observed also delayed reactions. No negative reactors were found to be passing eggs reported Alves and Blair (Lancet 2 556 1946) who considered the test more revealing than repeated microscopic examinations in finding cases and assaying results of treatment.

Swimmers Itch —The cercariae of *Trichobilharzia ocellata* and other avian schistosomes cause a characteristic pruritic dermatitis of bathers in the United States. Cort (J 90 1027 1928) recognized the nature of the condition when he experienced it himself as a result of immersing his forearms in water in which were recently collected snails. There occur (1) a prickling sensation which may begin while still in the polluted water (2) erythema, papules and sometimes pustules, (3) intense irritation for the first few days and (4) gradual disappearance of symptoms over a period of some 2 weeks. An exposed bather will suffer less if he wipes dry with a towel immediately after leaving the contaminated water (Brackett J 113 117 1939)



Fig 197 —Schistosome dermatitis After exposure, left foot was promptly wiped dry (Brackett J 113 117 1939)



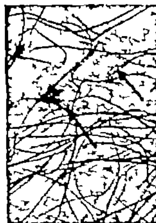


Fig 198.—Schistosome dermatitis Lesions produced by experimental exposure to the cercariae. (Cort 90 1027 1928)

Fig 199 —Penetration of follicles by cercariae causes inflammatory papules. (Dr Laird Lyster Institute of Pathology MacDonald College, Quebec.)

The worms are not parasites of man but rather of birds and mammals; their eggs in the feces of these animals hatch in water into miracidia which develop into cercariae in snails. Control may be accomplished by distributing CuSO on the beach * lb. per 1,000 sq. ft. of lake bottom, adding 70% fresh hydrated lime. The chemicals are disseminated by power pump and long rubber tubes reaching the bottom (the Michigan Plan; see Macy: NoW Med 51: 910 1952)

A Hawaiian marine larval schistosome tentatively identified a *Cercaria littor sal na* (Penner: JParasit 1 36: 466 1950) the adult form of which had not been discovered, is apparently the cause of Pearl Harbor Itch as described by Arnold and Bonnet (Proc HawaiianAcadSci 25: 4 1950) according to Chu (Sci 115: 151 1952) Clam diggers dermatitis seen in the Long Island Sound region seems probably to be due to schistosomes (O ris and Combes: AIDS 66: 367 1952)

Seabathers eruption characterized by erythematous wheals appearing a few *hours after sea bathing and persisting for several days itchy but without complications,* was carefully studied by Sams (AIDS 60: 227 1949) but the cause could not be demonstrated, despite the similarity to schistosome disease

Sa Cawston (JTropM 40: 103 1937) biologic control by cultivation of fish and rats and Brackett (WiscMJ 3 443 1938) swimmers itch in Great Lakes region; Thomas (FlaMAJ 26 87 1939) swimmers itch off Florida; Brackett (AmJHyg 32 86, 1940) snail host in Wisconsin lakes (JMJ 2: 61 1941) schistosome dermatitis; Porter (Larval Trematoda Found in Certain African Mollusca, Johannesburg, 1938 rev J 114: 682, 1940)



Fig 409—Schistosome cercariae, dark field illumination (Photographs by D M Blair from Gradwohl et al Clinical Tropical Medicine Mosby 1951)

superb parasitologic work on fluke infection of snails Miller (AmJPubH 31 385, 1941) swimmers' itch in Michigan Koppisch J 121 936, 1943) S m so passing through skin photomicrographs MacF lane (NZealMJ 43 136, 1944) swimmers' itch Gelfand and Osborn, abs JJD 57 73, 1946) early symptoms of schistosomiasis in Africa Thoma and Gage (BullUSAMD 4 107 1945) early symptoms S japonica; Winkenwerder (BullJHH 78 408 1946) S japonica in Leyte personnel Chang et al (J 136 230, 1948) cerebral granuloma due to S japonica Larf n (Tran RoySocTropM 43 169, 1949) pulmonary schistosomiasis, asthma, chronic bronchitis, emphysema Oli r (AmJHyg 49 154, 1949) skin penetration J rcho et V Barkalow (Geographic Review 42 212, 1952) swimmers itch in North America, Macy and Moore (Sci 115 650, 1952), 3 species of Trichobilharzia in Pacific Northwest Haemmerli Dermatologica 107 302, 1951) Zurich cases, photomicrographs Mitchell (AIDS 70 803, 1954) Ontario cases Kaw hry (AD 7 65, 1953) soft, cauliflower-like egetative, papillomatous, schistosomal granulomas, containing ova, found in late cases in perineal and genital regions

CESTODE INFESTATION

Cestoidea, a class of Platyhelminthes (compare Trematodes) are el el parasitic organisms covered with noncilli ted ntegument; adults hermaphroditic; embryos hatched from eggs; scolex provided with suckers and frequently with hooks for attachment to host no digestive tract; body usually divided into separate, sexually complete units called proglottids All human tapeworms, including *Taenia solium* and *Echinococcus granulosus*, fall within the family Taeniidae of the order Cyclophyllidea in the subclass Cestoda. It is interesting to note that Atabrine is effective against tapeworms (Paeckelmann: DeutschesMedJ 5: 244 1954)

Cysticercosis.—*Cysticercus cellulosae* the larva of the cestode *Taenia solium* causes in man small rounded firm, subcutaneous tumors painful and larger while the parasite is alive and actively irritating but painless, smaller and sometimes calcified after its death. Rarely the lumps become abscesses (Dixon and Hargreaves: QJM 13: 107 1944) The verminous tumor may occur in practically any part of the body 10 cases in the central nervous system were collected by Chung and Lee (ChinMJ 49 429 1935) Atabrine, preceded by a purge with castor oil or magnesium sulfate cured 11 cases of gut infection with the adult worm for Sodeman and Jung (J 148: 285 1952)

Echinococcosis.—*Echinococcus granulosus* (Goeze, 1762) lives in man only in the larval state. The adult worm is only 3 to 6 mm. long and inhabits the gut of dogs particularly The eggs reach the stomach of man by fecal contamination, and the embryos are freed. They generally infest the liver by way of the portal system but may reach any part of the body In subcutaneous tissues, the lesions are walnut to apple-size semitranslucent tumors. The treatment is excision, exerting extreme care to avoid rupture of the parasitic cysts. Some 8% of cases of echinococcosis show subcutaneous lesions. Urticaria, fever pruritus, erythema and hyperhidrosis are among the cutaneous symptoms due to allergy (Godfrey AnnIntM 60 783 1937)



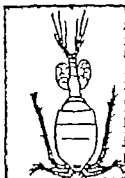


Fig. 601.—*Sparganum* larva of cestode, in eyelid of Annamite girl. (Dr E. Brumpt.)

Fig. 602.—*Cyclops viridi* (×10) intermediate host of Dracunculus (By permission from Medical Entomology by Drs. W A Riley and O. A. Johannsen, McGraw Hill Book Co., Inc.)

The cyst fluid is potently allergenic and may be used for intracutaneous diagnosis. The skin test (Casoni s) sensitizes and should be used but once (Rist PresseMéd 47 201 1939) It failed in the diagnosis of 5 of 27 cases of Kneebone (MJAustral 1 201 1937) See also Fairley (MJAustral 1 472, 1929) and Culbertson and Rose (JClinInv 20: 249 1941) A complement fixation test is also of some value (Rose and Culbertson J 115 594 1940)

Sparganosis.—A sparganum is a larval form, the adult usually being unknown of a pseudophyllodean cestode. Spargana may be found in the subcutaneous tissues and muscles of various vertebrate hosts. Human infection may result from ingestion of larvae and their migration to subcutaneous tissues and further development there or from migration from infected flesh directly into human tissues. The worms are elongated, ivory white ribbons, inducing in infected tissues edema, pain and itching The region of the eye is often involved in French Indo-China Surgical removal of the animal is curative

D mansonoides is perhaps the source of the nonproliferating type of sparganosis found in the United States (Craig and Faust 1951 p. 561) Infestation may be avoided by drinking clean water and not ingesting raw tadpoles or poulticing sores with polluted raw meat, unhygienic habits which can be eliminated from natives by education. See Castellani and Chalmers (Tropical Medicine 1929 p 606) Feng and Hoeppli (ChinMJ 50 1457 1936) Feng et al. (ChinMJ 54 530 1940)

ANNELIDA

Leeches.—Roundworms of the phylum Annelida include the class Hirudinea, the leeches, the bites of which are of dermatologic interest. The leech maintains the flow of the blood it sucks by introducing an anticoagulant albuminose hirudin into the skin (Q.M.N. J 172 184 1946). The leech is likely to be discovered by the dripping of blood from the bite, which is painless, but the wound is slow to heal after the animal is removed. A leech may attach itself to the skin or to the mucous membrane of the upper respiratory tract, pharynx, esophagus or conjunctiva. When it is fully gorged it drops off, but it should not be pulled off lest the jaws remaining in the wound incite severe inflammation or secondary infection. To hasten its release one may apply strong brine, alcohol or vinegar to the site of attachment, or apply a lighted match to its body, or cocainize the head and remove the slippery body gently and carefully from a nasal passage. There is the hazard of its falling into the trachea, and the patient should be placed head down when a leech is removed from the nose or throat.

Attack can be avoided by wearing suitable protective clothing, by impregnating the clothing with dimethyl phthalate, and by boiling the drinking water. *See Craig and Faust (Clinical Parasitology, Lea & Febiger 1951, p. 606).*



Fig. 501.—Leech bite on forearm. (Dr. Clyde Cummer.)

ARTHROPODA

The phylum Arthropoda consists of invertebrate, segmented, bilaterally symmetric animals. Their bodies are composed of more or less well-differentiated parts enclosed in a chitinous frame, and the paired extremities are articulated. They possess a complete digestive tract with mouth and anus, a blood system, a central nervous system with brain and with paired nerve trunk and ganglia for each segment, and separate sexes. The classes **Arachnida** and **Insecta** include all parasites of man. The class **Diplopoda**, millepedes, consist of fangless nonvenomous animals with pairs of legs for most segments. The class **Chilopoda**, centipedes, possesses a single pair of legs per segment, the first pair modified to form poison claws. A Texas representative *Scolopendra morsitans*, can kill mice and *S. cingulata* venom produces painful edema and papules in human beings. Urticarion and purpura constitute the maximum of their maleficence, and they cannot bite through thick epidermis. Now and then one wanders into the nasal passages and sinuses. The class **Crustacea** contains a few eucopepods, such as Cyclops, which serve as intermediary hosts of worms of consequence to human beings. An outline of arthropodan dermatoses was given by Canizares and Shatin (ADS 68 157 1953). See general references on diseases due to animals.

Arachnida are terrestrial arthropods with tracheal or cutaneous respiration, the body being formed, in general, of 2 parts: the anterior (cephalothorax) bears the mouth and 4 pairs of legs, and the posterior part (abdomen) includes the anus. Some members of the class bite or sting. This class includes the **Arthrogastra**, the orders of which have distinctly segmented abdomen (scorpions, pedipalpida, solpugids or pseudoscorpions, and harvestmen) and the **Sphaerogastra**, spiders proper which lack distinct segmentation. **Araneida** (spiders) and **Acarina** (mites and ticks) are orders of sphaerogastran arachnids.

Pedipalpida, whip scorpions, are more feared than the facts justify. Vesiculation has resulted from crushing a specimen upon the skin.

Solpugida are spiderlike forms lacking a true cephalothorax. The fangs can produce wounds, but venomousness is wanting.

SCORPION STINGS

Scorpionida, true scorpions are mainly tropical. They may reach a length of 8 inches and are pre-eminently predaceous creatures which lie hidden by day and hunt by night. Most true scorpions of the United States are of little significance, the sting of *Centruroides vittatus* the common one, for example being no more severe than that of a bee. Some species found in the southern part of the United States and throughout Mexico are decidedly dangerous. The clear colorless toxalbumin introduced perhaps into a bare foot, produces intense pain numbness, sweating salivation, rapid pulse shallow respiration, fever convulsions and even respiratory paralysis and death especially if the victim is a little child.

C suffusus is the common Mexican species. Deadly species in the Southwestern U.S.A. are *Centruroides sculpturatus* and *C gertschi* which reach an adult length of about 3 inches and are to be described as long and slender with delicate-appearing pinchers and a small thornlike structure at the base of the stinger.

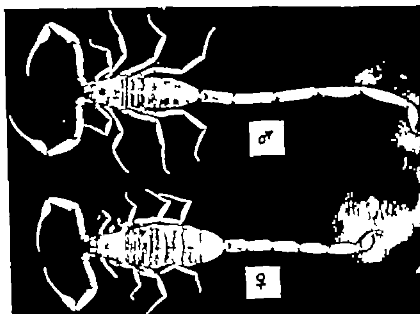


Fig. [illegible].—*Centruroides sculpturatus*. (Courtesy of Herbert L. Stahnke, Ph.D., Arizona State College, with permission not to be copied.)

Effects of the sting were graphically described by Stahuke (Scorpions, Arizona State College Tempe 1949)

> Immediately after being stung, one experiences a prickly pin sensation which may become quite painful. The spot becomes hypersensitive so that bumping it causes additional tingling sensations. A sort of prickly pin sensation and numbness travel up the extremity leaving the part or the pathway with a woody feeling. Severe tingling and electric sensations may be experienced throughout the whole body. This venom does not produce a swelling or discoloration at the site of the sting. A feeling of tightness develops in the throat, and the tongue may develop a feeling of thickness so that tiny children will try to reach into the mouth to remove an imaginary obstruction. There may be a difficulty in speaking, and a restless or [ ]itt ry feeling develops. In adults this may or may not lead to slight, involuntary twitchings of the muscles; small children in this stage will not be still, and often attempt to climb up whatever conf[ ]es them. The restless condition may lead to a series of sneezing spasms accompanied by copious salivation and nasal fluid discharge. The restlessness may develop into a severe convulsive state sometimes with curious activity of aimless crawling while bent forward, followed by backward bending of the trunk, that is usually rhythmic. The arms may be flailed about, and breathing is labored, with pronounced wheezing. This activity may last for from 45 minutes even to 12 hours, leading to acral cyanosis and death. When recovery

takes place the last part of the body to become free of the effects of the sting will be the part actually stung and this may be hypersensitive for several days so that jarring it evokes tingling or painful sensations.

Treatment advocated by Stahnke requires the prompt application of a tourniquet proximal but close to the sting Ice the site then pack the entire part in crushed ice and water The tourniquet is removed after the tissues have been refrigerated and within 5 minutes. Immersion in ice water is kept up for 2 hours. Definite swelling then present indicates that neither the deadly scorpion nor black widow caused it and, if so immersion in ice water is no longer needed Antivenin or other medication is not necessary unless definite symptoms of poisoning are present When possible the offending animal which produced the sting should be saved for identification. Incision of the site of the sting is erroneous. Supportive measures of all kinds may be appropriate including oxygen inhalation, artificial respiration and anticonvulsant therapy *Do not* give Demerol (Stahnke ArizMed 11 51 1952)

ACTH has been tried. I have seen notable relief in acarine intoxication with the adrenocortical drugs. Cortisone was successful in a case of Maretic (J 152 609 1953)

Antiscorpion serums have been developed but are often species-specific and so therapeutically helpful only in limited regions where particular species are prevalent (Craig and Faust 1951 p 642) No immunity develops following repeated stings. The only prevention lies in avoiding the animals.

See Hoffman (AnInstBiolMex 2 291 1931 3 42, 1932) scorpions of Mexico de Magalhaes (JTropM 41 393, 1938) Brazilian Kent and Stahnk (SouthwestM 23 1?, 1939) southwestern U S A. Ansari (BMJ 388, 1948), gangrene of terminal phalanx followed sting Celoria and Sloe (bs J 139 1119, 1949) abnormal EKG from scorpion; Brazil Letter (J 155 1363 1954) extermination with benzine hex chloride spray

ARANEIDISM SPIDER BITES

All true spiders produce venom but few have fangs able to pierce the skin or venom potent enough to produce more than transitory irritation (Craig and Faust) The tarantulas despite their dreadful appearance are essentially innocuous. The genus Latrodectus, relatively small spiders of the family Theridiidae are the ones to be feared. Species occur in almost every country and *L. mactans* the black widow is the member of consequence in the United States southern Canada, Cuba Mexico and elsewhere in the Western Hemisphere

L mactans is coal black, with orange or scarlet markings. The male is about 6 mm long the female about 12 mm The abdomen is globose and has an hourglass-shaped reddish spot on its mid venter These spiders spin coarse tough webs about old lumber under outdoor privy seats in garages and basements and in trash piles, where they should be carefully avoided in order to prevent bites.

The bite is painful and the site becomes swollen and perhaps purpuric, soon there occur general symptoms of intoxication including twitching and tremor numbness vomiting sweating aching abdominal cramps that may falsely suggest the urgent need for surgery (Wilson Surg 13 924 1943) and even shock or delirium While the symptoms are sometimes exceedingly violent, actual fatalities have been few

In treatment repeated intravenous injections of 10% magnesium sulfate are advised (Davis J 130 783 1946) Atropine morphine, pituitary extract or epinephrine may be indicated. Calcium gluconate 1 to 2 Gm. intravenously given at once will usually relax muscle spasm (Miller J 139 1238 1949) and provide better relief than morphine The antivenin should then be given after testing the patient for allergy to horse serum from which it is prepared (NNR J 129 1017 1945) and desensitizing him if necessary This Sharp and Dohme preparation has value if given early enough (Kirby-Smith

SouthMJ 38: 696 1945) Prior to its introduction convalescent serum was found to contain antibodies and possess therapeutic effects (Gray CalifWMed 43 328 1935) The intramuscular injection of 2 cc. 1:2000 neostigmine methyl sulfate accompanied by 1/150th grain of atropine will relieve promptly according to Bell and Boone (J 129 1016 1945) confirmed by Holloway (ArkansMSJ 47: 75, 1950) Immediate incision and suction may be tried One may flame the site of the bite at once with a burning match head and so prevent aftereffects (J 122 208 1943) Spraying the web with 10% DDT in kerosene results in death of the spider (Van Riper Sci 104 111 1946)



Fig. [illegible]—Black widow spiders (females) *Latrodectus mactans*. From the collection of V Lewhim, (Merck Report, July 1946, from article by Herbert L. Stahnk : Some Poisonous Animals of the United States; by permission of the author and publisher)



Fig. [illegible].—Spider bite on leg, species not identified; not unusual in Missouri.

Necrotic Arachnidism was described by Witkind of Montevideo (abs J 153 1552, 1953) as consisting of cutaneous necrosis, progressing to dry gangrene at the site of the bite, fever jaundice, hemoglobinuria, cutaneous and intestinal hemorrhages, exanthema and hemolysis. It is a serious condition and is fatal in a high percentage of children. A spontaneous regression of the acute symptoms occurs between the fifth and seventh days; local necrosis follows a slowly regressive course. In 2 cases which proved fatal, the spiders were captured in the act of biting and were identified as females of the *Loxosceles laeta* species. *Loxosceles laeta* spiders are common in certain cities of Uruguay and other countries of South America, and it is their bite which produces the necrotic, eruptive and icterohemolytic forms of arachnidism.

Spiders of undetermined species produce painful bites which are followed by central necrosis and an erythematous sometimes vesicular areola measuring a few inches across. I see such cases once or twice a year and may prescribe the topical application of tetracycline ointment. On the legs such lesions have been followed by the development of chronic lichenoid dermatitis. Compare gangrenous spot of Chili, described by Macchiavello (PuertoRicoJPubHealth 22: 425 1947)

See Baerg (JParasitol 9 161 1923) experimental black widow bites of rat and human; Bogen (J 86: 1894 1926 ArchIM 38 623 1926, AnIM 6 375, 1933) complete study bibliography; Trolse (ComptrendHebdol 89 1422, 1928), antiserum; Blair (ArchIntM 54 831 844 1934) life history of L. mactans, Gilbert and Stewart (AmJMedSci 189 532 1935) calcium gluconate; Frawley and Ginsburg (J 104 1720 1935) description, bibliography MgSO₄ therapy; Hargis (NEngJM 215 488, 1936), Georgia cases treated with calcium, morphine dextrose hot bath; Finlayson (J 106: 1406, 1936) South African L. concinnus and L. indistinct and Australi L. hasseltii resemble L. mactans; Villard (La Venin des Araignées, Masson, 1936); South American species, antivenin, monographic; Anon. (Ill. Med. 54 2191, 1939) mating infestation of a ship; Noon and Mi ear (SouthwestM 25: 169 1941) antivenin; Kirby-Smith (AnnSurg 115 249, 1942) death actually rare generally recovery in 3 days or less; Gajardo (Ibid 115 1259 1942) South American experience; Frank (MilSurg 91 329 1942), military personnel in Carolina maneuvers; Sampayo (Latrodectus mactans y latrodectismo, Buenos Aires 1942, 217 pp., 48 illustr.) comprehensive monograph; Thorp and Woodson (The Black Widow: America's Most Poisonous Spider Univ N C Press, 1945) popular style authoritative; Greer (NEngJM 240, 5, 1949) burning of soles typical feature; Tinkhaus (NCarolMJ 13 37 1952), clinical; Courie (SouthMJ 45: 1193, 1952) epinephrine injection; Goudy and Masters (JOklaMA 47 309 1954) cortisone apparently beneficial in 2 cases.

ACARINE PARASITISM

Mites have globoid bodies formed by the fusion of the cephalothorax and abdomen. They have 4 pairs of extremities in the adult state; the larvae are hexapod. The terminal segment of the legs possesses organs of fixation: hooks, claws, or pediculated suckers. Many are parasites. Of the order Acarina, superfamilies containing members of dermatologic interest are **Ixodoidea** (ticks), **Sarcoptoidea** (itch mites), **Tyroglyphoidea** (food mites), **Demodicoidea** (follicle mites), **Parasitoidea** (parasitoid mites), **Tarsonemoidea** (mites of grain itch) and **Trombidoidea** (chigger or red mites).

TICKS

Ixodoidea are large mites covered with a leathery integument and adapted exclusively to blood-sucking from mammals, birds and reptiles. The family Argasidae are soft bodied and the Ixodidae are hard bodied.

Argasidae.—Ticks of the genus *Ornithodoros*, some 30 species of which parasitize a variety of birds, mammals and even reptiles, infest nests and beds of their hosts, commonly dirt-floored thatched huts of man. They feed intermittently. Most of them bite painfully and provoke persistent, firm, itchy papules. *O. moubata* inoculates African tick fever with its bite. *O. hermsi* transmits relapsing fever in California. *O. turicata* is the vector of sporadic recurrent fever in America.

Ixodidae are vectors of great medical interest because in numerous localities they transmit to man various spirochetoses, rickettsioses and tularemia; and they may cause tick paralysis, sometimes fatal, as well as local inflammatory accidents.

Ixodidae are hematophagic in all stages of their evolution. They feed throughout the year or only at some seasons according to climatic condition and their host peculiarities. Each species seeks certain hosts by preference but when these are not available they content themselves with accidental hosts. *Dermacentor andersoni* and *D. variabilis* are vectors of Rocky Mountain spotted fever and tularemia. *D. occidentalis* the Pacific coast tick has transmitted tularemia.

Tick Bites.—The biology of ticks and the tissue reactions to them were discussed by Winer and Strackosch (JID 4 249 1941). The site of the bite is marked early by edema and eosinophilic infiltrations, later by mast cells. A dermal nodule may remain unresolving and have to be cut out.

Tick bite granulomas resemble the nodular dermal fibrosis histologically showing an eosinophilic granuloma, appearing sometimes as late as 10 weeks after the bite and persisting as an itchy eczematoid lesion or a pink, painless nodule 1 cm. or so in diameter (Allen AmJPath 24 367 1948 Tobias JID 12 255 1949). Similar nodules may occur in scabies (p. 606).

D. variabilis evidently by envenoming the skin of the occipital region, produced alopecia of motheaten appearance in 2 children observed by Ross and Friede (AD 71 524 1955).

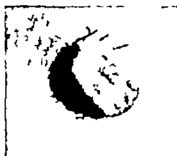
To remove a tick, one may touch it with tobacco juice, kerosene, a hot nail or one of the essential oils, thus inducing it to remove itself. The cutaneous lesions are urticarial and itchy but themselves usually inconsequential.

Avoidance of tick infested regions is important in avoiding tick transmitted disease (see Rocky Mountain Spotted Fever) Repellents are useful (see Chigger mites, treatment)

Tick-Bite Paralysis.—Motor paralysis due to the bite of a tick and relieved by the removal of the tick has been observed in man and animals. The condition affects children as a rule There are observed weakness of sudden onset ataxia, motor palsy clear conscious mental activity afebrile intoxication, and paralysis progressive even to a fatal termination unless the tick is removed. Its removal is followed within 48 hours by recovery *Dermacentor andersoni* and *D variabilis* are the usual offenders reported the venom rather than the function as a vector is responsible.

TICKS.—Davis (PHRpts 54: 1345, 1939), *Ornithodoros parkeri* transmission of relapsing fever; Brunet (BJVD 15 63, 1939) *D andersoni* embedded in penis, requiring dissection Pasternack (J 112 1814, 1939) tularemia following tick bit Cooley and Kohl (PHRpts 54 44 1939), key to Amblyomma in U S A.; Woodland et al (J 122 1156, 1943), tick bite fever in Texas (see endemic typhus) Cooley nd Kohls (The Argasidae of N Amer Central Amer nd Cuba, Uni Press, Notre Dame Indiana, 1944) Feder (J 126 292, 1944), fever and secondary infection complic ting tick bites Cooley (The Genera Dermacentor and Otocentor [Ixodidae] in the U S. A., Nat'l Inst. Health Bull. #171 Supt. Documents, Washington, D. C.)





Figs. 307 and 308—Tick attached to kin, simulating seborrheic keratosis (Wiener J 112 1404 1939)

TICK BITE PARALYSIS.—McCormack (J 77 260 1921) case in young woman, quotes Borthwick (Veterinary J London 7 32, 1905) paralysis in sheep Nuttall (Parasitol 7 95, 1914) Barnett (J 109 846, 1937); Robinson and Carroll (J 111 1093 1938) *D variabilis* case, M lherin (JPediat 16 36, 1940) Abbott (PMMC 18 39; 59 1943) review Dawson et al. (AmJDisChild 79 491 1950) Kittrell (J 147 1661 1951) Alexander (J 149 931, 1952)

ITCH MITES
SCABIES ANIMAL AND HUMAN

Sarcoptidosis.—In scabies resulting from infestation with mites whose natural habitat is other than human the peculiar restriction and specificity of the relationship of parasite with host is such that the acari do not thrive and multiply Thus the harboring by man of an animal mite may be unpleasant, but it is not serious (Toomey UCutDis 25 705 26 473 1922) See Stigter (abs J 154 722, 1954); Booth and Jones (ADS 69 531 1954) mites in industry

Some occasionally involve human beings and live on them for a time provoking the itch temporarily The absence of burrows is noteworthy in all of these types. They produce diffuse and pruritic miliary or polymorphous eruptions and either heal spontaneously or are easy to cure See Brumpt (1949 p 1215)

S minor (Fürstenberg 1861) ar cati	from arious rodents and carnivora. Mild in man taken from cat, it persisted a fortnight
S. scabiei var aucheniae	from llama
S scabiei var cameli	from camels or dromedaries (may be severe)
S scabiei var canis	from dogs; disappe rs spontaneously (dog scabies may be indistinguishabl from human [Toomey])
S. scabiei var caprae	from goats may be severe
S scabiei ar lupi	from wolf
S. scabiei var equi	from horse, ass and mule. Slightly larger than that of human being Burrow re not present, but the cari bound in scales and crusts.
S scabiei var leonis	from lion
S. scabiei va ovis	from sheep
S scabiei va suis	from pig; mild, nd heals easily
S scabiei va vulpis	from fox. Infestation from skinning animal

Sarcoptosis of Animal Origin, contracted from horse mule or ass is acquired by direct contact with sarcoptic mange in these animals and is manifested with prompt itching soon followed by papules and urticaria, with worse symptom at night than in the day. *The face scalp, external genital axillae breast and interdigital areas almost invariably* remain free. The forearm suffer most and the arms, neck and ones of restriction by clothing are involved. The burrows are very short the vesicles are comparatively large and erythema, with or without urticaria, is widespread and severe. Crusting may occur and pigmentation may result. Th disease resembles that produced by harvest mites. It requires treatment a for ordinary scabies.

Cat scabies causes serious, ven fatal disease in the cat affecting particularly th head and external ear. In man there may occur limited patches of papules on the neck, circumscribed, or gradually extending in bizarre fashion so a t incl d the sides of the trunk and thighs, but avoiding hairy areas. Erythema, tiny papules and tough little apical vesicles are seen. Itching is continuous and worse at night. The hands, buttock and external genitals are not affected (Davies: BJD 53: 18 1941). Infestation of man may result also from the handling of mangy rabbits (Kaufmann: AmJCli Path 1 601 194).

Chorioptosis, fetlock scabies du to *C communis* (Gerlach 185) occurs in horses, oxen sheep and goats. The parasite lives in colonies in long hair. The disease it produce begins generally above the hoof in the horse and spread upward rarely so far as to the belly. It develops slowly is worse in winter and causes abundant epidermic desquamation. Tuft of hair pull out and leave the skin bare and smooth; later it becomes crusted, fissured and bleeding. In man there is provoked severe erythematopapular dermatitis of short *duration, involving the hand wrists area of contact rarely generalized. Thi acute form* i sual a rare chronic generalized papulocrustaceous form ha been described (Menger 1896)

Chorioptes symbiote a *bovis* (Verheyen, 1862) ha been found on the head of human beings ca si g f w s mptoms.

Psoroptosis, cattle scabies, due t *P communis* in oxen sheep horses and cattle producing thick scales and severe pruritus but no burrow. It does not propagate on man, where the first instance w recorded *by* L. Wilson in 1843 th mite i barely visible wh ti h spot on hair or epidermal surface

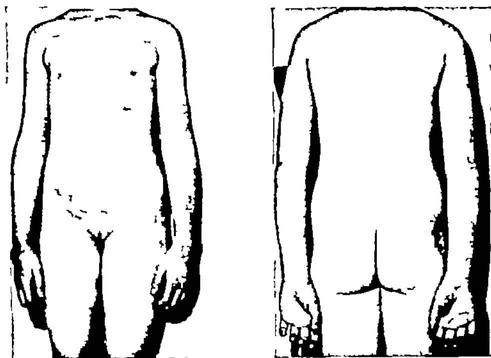
See Warburton (Parasit 12 265, 1920) rieties of sarcoptic parasites in ma and nimal Buxton (Parasitol 13 146 1921) taxonomy, Widman (ADS 5 675, 1922) *S scabiei ar hemi* is from orangouta g Goldman nd F klman (ADS 59 1 3, 1949) Siamese gibbons with disease resembling Norw gian scabies i fected human being. Fisher et al (ADS 63 328, 1951) *Dermatoph goides scheremetewskyi* found on boy with *T purpureum* infection, also on scalp of a zoology professor and members of his family pathogenicity l bious, ha been found i urine

Scabies (**The Itch**) the infectious disease due to *Sarcoptes scabiei* var *hominis* is characterized objectively by intraepithelial burrows made by the female for depositing ova. This results in intense itching and in multiform lesions due to scratching. Secondary coccic infection is common

S scabiei var *h m n s* (Linné 1758) Female pearl gray o pinkish about 330 μ long, 300 μ across oviparous. Male pinkish, about 225 μ by 175 μ. Venomous salivary gl d open i the buccal cavity. Ovum bearing female inhabit th end of the burrow wh h he has made in the epidermal laye. Mal also ma li e in the burrow o more often, outside the burrow u der the epidermis. Egg laid by the f male measure 150 by 100 μ. Those farthest volved are those farthest from the female located of course neare the orifice of th burrow. De elopment takes place in 4 stages: (1) day after be g laid, the o um becomes a hexapod larva. It h tches i the burrow which it promptl lea es t live on the surface of the health skin. It enlarges and undergoes several moults. ( ) D th xteenth da th nimal mo lts agai and gives rise to an octopod n mph which li es n the cust on the kin. (3) Another moult, which occurs about the twenty eighth day set free pubescent mal and female animals. (4) Following the final moult wh ch occurs about the sixth week the pubescent a d fecund female develops a ew orifice which serves f r the laying of eggs. She the forces herself into the skin producing a characteristic burrow in which she lays eggs.

See Munro (JRoyAMC 32 1 1919) W burton (Parasit 12 265, 1920) Sarcoptes arieties i man nd nimals Buxton (Parasit 13 146, 1921 BMJ 2 39 1941), Friedman (Biology of *Acarus* cabiei, Froben, 1942) Heilesen (ActaDV 26 I Suppl. 14, 1946) Baker and Wharton (An Introduction t Acarology M cmillan, 1952)

Symptoms.—Itching worse at night is the main complaint. The areas *of predilection are the dorsal aspects of the interdigital webs, flexures* of the wrists, axillary folds, lower abdomen, buttocks, genitalia and ankles. In infants the palms and soles frequently are involved. Other parts of the body also are occasionally attacked but the face and scalp escape except in infants.



Figs. 309 and 310.—Scabies.



Fig. 311.—Scabies: typical excoriated papules.



Fig. 812.—Scabies with secondary infection of hands. (Dr. Sam'l Sweitzer.)



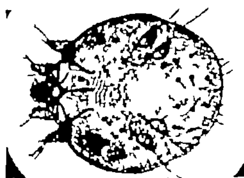


Fig. 814.—*Sarcoptes scabiei*, female. (Dr. Fred Weidman.)

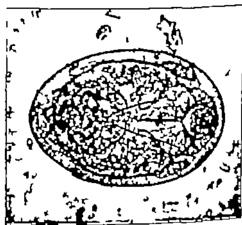


Fig. 815.—Ovum containing larva of *Sarcoptes scabiei*. (Dr. Fred Weidman.)

Fig. 813.—Scabies. (Dr. George M. MacKee.)



Figs 616-618.—Scabies (Dr Robert N Andrade)

Fig. 619.—Scabies, typical penil lesions. (Dr Sam [illegible] [illegible]altzer)
Fig 620.—Norwegian scabies (Beatty BJD 25 [illegible], 1912.)

The lesions, consisting mainly of small excoriated papules and vesicles, are seen on close examination. Tiny cuniculi or burrows can usually be found. These appear as whitish tortuous or zigzag superficial, threadlike channels. The closed end is marked by a tiny grayish speck the resting place of the female parasite The burrows are a few millimeters long and are most numerous on the interdigital webs mammary region in women and shaft of the penis in men. The disease is slowly but steadily progressive as a rule and, if neglected involvement soon becomes more or less general In cleanly individuals the eruption usually is scanty and impetiginous or urticarial manifestations may overshadow those of scabies.

Experimental Inoculation of Scabies.—Observing the course of self inoculation with a single female acarus Clayton (BMJ 1 752 1944) noted that she crawled about 1 cm then burrowed in, rapidly at first and was entirely within the epidermis at the end of an hour She thereafter traveled 1 mm in 2 days. *Itching began after 3 more days and became intense within* another 2 weeks. By the fourth week scattered lesions began to appear Since the life cycle is accomplished in from 7 to 13 days propagation to the stage of clinical disease takes at least 3 weeks. The symptoms and gross signs appear only after the patient has become sensitized to the mite but following a second infection the patient responds with inflammation and itching immediately (Mellanby Scabies, Oxford Univ Press 1943 MacKenna BMJ 2 287 1950)

Norwegian Scabies. —In neglected cases of long duration the number of acari may become enormous with extensive crusting and the disease may involve not only the trunk limbs, palms and soles but also the face and scalp. Itching is not necessarily present and such a case pruritus absent was described in an uncomplaining moron by Sweitzer and Winer (ADS 43 678 1941) The assertion that scabietic infection occurs by predilection among the mentally deficient (Hodgson BMJ 1 316 1941) led to lively disputation and psychometric testing with the view becoming widely accepted that the parasite is unconcerned with the intellectual capacity of the host (Mellanby et al. Lancet 2 596 1942) Crusted scabies, the name Colnan (BJD 62 71 1950) prefers to Norwegian does not generally itch much really is associated with mental deficiency and is productive of hyperkeratotic lesions of hands and feet and involvement of the face and scalp which escape infection in ordinary cases. There is some question as to whether the mite in crusted scabies is identical with the ordinary one (Anderson BMJ 2 25 1952) Swarming with parasites estimated at 10 000 per cc. of crust (Grutz Dermatologica 97 279 1948) the disease is highly infectious and requires isolation. In fact, cross-infections often lead to the correct diagnosis in cases originally not recognized (Wells BMJ 2 18 1952)

Complications of scabies include secondary infection (impetigo ecthyma furunculosis cellulitis erysipelas, infectious eczematoid dermatitis) medicinal *dermatitis venenata, urticaria and dermographia insomnia and psychosomatic* reactions such as delusion of parasitism and neurodermatitis (Allison NoWMed 38 23 1939 Goldman WarM 5 294 1944) Secondary infection will not clear until the animal parasites have been eliminated after this has been done antibacterial medication is likely to prove unnecessary I have wasted some penicillin as well as antihistamine drugs on some cases of scabies, a disease not always textbook Albuminuria observed during scabies was thought to be coincidental by Niles (ADS 38 19 1938) but it might be incited by secondary streptococcic infection, as seen by McIntosh (JIowaMS 33 181 1943) while Wang et al. (ChinMJ 66 277 1948) reported a number of cases of acute glomerulonephritis (p 282) in secondarily infected patients.

There occasionally occur large papules, oval elevated and hard, of a reddish or bluish red hue early later losing the bright color and often presenting central bluish black hemorrhagic crusting (Cremer abs YBD 1948, p 357) These lesions, few in number appear where the epidermis is thin,

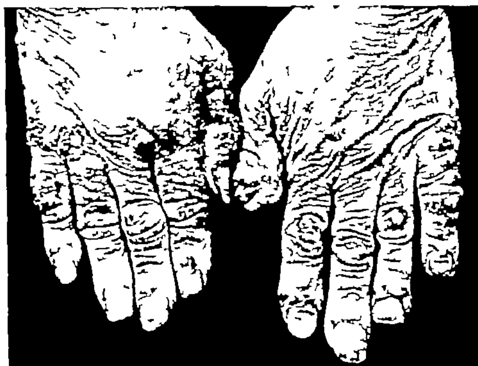


Fig. 821.—Norwegian scabies. (Dr. O. G. Costa.)

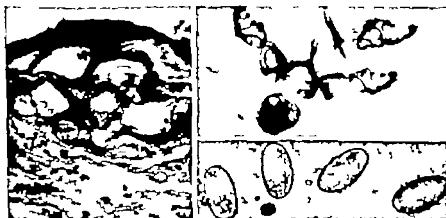


Fig. 822.—Norwegian scabies section shows numerous burrows in superficial epidermis and empty shells of ova scybala are seen as solid black lumps. (Dr. Fred Weidman.)

Figs. 823 and 824.—Above are recognizable parts of exoskeleton of *Acarus scabiei* such as may be identified in a scraping. Below are ova. (Hand, USNMB 46: 834, 1946.)

especially in genital mammary and axillary regions, and they harbor the mites and persist for months, perhaps promoting recurrences despite treatment They are seldom seen in untreated cases. They may become pyodermic and may require excision for cure Compare Tick bite granuloma

Diagnosis.—The distribution of the lesions is suggestive The head is not involved in adults a distinction from dermatitis herpetiformis. The hands may escape but the anterior axillary folds in both sexes, the waist the nipple region in the female and the shaft of the penis in the male should be scrutinized. The interscapular region is free In babies the soles, palms, scalp and flexures of the wrists usually are involved Nocturnal itching is typical when asked if he itches more in the daytime the patient is likely to answer in the negative with vehemence he itches at night Persons in close association with him are likely also to be infected. The discovery of burrows is seldom impossible although it may be somewhat difficult (Stokes J 106 674 1936) The unclad patient under examination is likely to manifest goose flesh (Semon and Barger BJD 29 173 1917) An infant lying in its crib rubbing its soles together probably has scabies (Dennie's sign) Lesions may be limited to the penis (Gilman ADS 52 83 1945) Exudative *erosion of the scrotum is perhaps scabietic Impetigo of the buttocks is almost* pathognomonic of scabies (MacCormac BJD 29 141 1917) A scabietic individual may complain of and manifest only urticaria until meticulously searched for evidence of parasitism

The mite or its products are usually easy to demonstrate

A dissecting microscope is a great aid to one who is not nearsighted. One searches the likely areas of interdigital web or flexure of wrist for a burrow At the end of it is the tiny whitish globule of the mite beneath the epidermis, or at least the pit where this should be With a needle point inserted along the burrow one dissects the epidermis and the mite adheres to the tip of the instrument Transferred to a slide it may be seen crawling vigorously and may be exhibited to the patient in order to secure his cooperation with the treatment to be prescribed if one is sure that the patient will be edified by the marvel rather than sickened.

Scrapings examined in 10% NaOH may enable one to identify parts of mites, eggs, moults or scybala (Friedman PaMJ 47 39 1943) This technic is illustrated in the articles of Hand (USNMBull 46 834 1946; JMichSMS 47 519 1948) KOH solution applied to the site selected for scraping prior to obtaining material enables one to obtain material containing microscopically identifiable debris (Hellier BMJ 1309 1945) If one paints likely places for burrows with a solution of fluorescein in glycerol and alcohol, burrows if present are penetrated by the fluorescent fluid and show as luminous streaks under Wood's light (Hirschfeld ActaD-V 26 4 1946)

In pediculosis corporis, the parasite or its ova can be found in the seams of the underclothing the hands and feet are unaffected, and the interscapular area is usually the site of numerous long excoriations. Nonscabietic dermatitis frequently involves the palms and soles and the face there is no history of familial infestation, cuniculi are absent the distribution of the eruption seldom simulates that of scabies and nocturnal aggravation of itching are absent

Errors in diagnosis arise from failure to suspect the infestation, or to recognize its complications, or to recognize it itself; interdigital and penile burrows, nocturnal itching distribution of the eruption and identification of the source are features one may depend on.

Epidemiology.—Close personal association and lack of cleansing facilities enhance the liability to infection. War conditions increase its incidence School children pass the parasites to one another and bring them to their families. Mediate transmission probably does not occur and disinfection of clothing is unnecessary (Shand BMJ 1 98 1944) Clothing impregnated with DDT does not prevent one's acquiring the infection (Hellier BMJ 2 555 1945)

Why the disease is now actually rare in North America is unknown (Epstein AD 71 193, 1955) I have not picked an acarus from a patient of mine for several years.

Treatment.—The cure of a case of scabies depends on the external use of parasiticides. Impetigo due to scabies does not contraindicate such therapy Sulfur is a reliable agent, and hexachlorocyclohexane benzyl benzoate beta naphthol, pyrethrum derris derivatives and other chemicals can be used successfully

The parasite is not hard to kill, success depending largely on the universality of application of parasiticide to the host overlooking no solitary

acarus. *S scabiei* is an obligate parasite on the human being It does not live longer than a few hours on intermediary objects. Overtreatment is to be avoided. A method I use may be outlined as follows

℞	Phenol	1.0
	Salicylic acid	6.0
	Sulfur precipitated	10.0
	Petrolatum, to	120.0

Do not refill.
Sig: Salicylic acid-sulfur ointment for scabies.

1. Begin treatment with a hot bath, using nonmedicated soap generously *Dry* skin. Then rub in ointment gently from neck down covering the *whole* body palms and soles, fingers and toes.

_ Rub in ointment morning and night for * days On the final morning take a soap bath and change all clothing and sheets.

2. Use the same sheet and the same underwear until the third sulfur ointment application is finished and you have cleaned off the ointment. Launder everything and start fresh. Ordinary lau dering suffices. *Do not* use more sulfur ointment unless so directed.

Lesions may persist and itching continue, despite successful attack on the mites themselves. This persistence of irritability must not of itself be considered justification for a repeated course of the parasiticide for contact dermatitis would result. It is to be allayed patiently with aluminum acetate baths, phenolated calamine lotion and barbiturates until 2 weeks have elapsed, by which time cure has generally proved subjectively satisfactory However if recognizable scabies still persists the patient is retreated.

Benzyl Benzoate (Nielsen s method: Kissmeyer: Lancet 1: 21 1937; Currey: CanadPHJ 30: 294, 1939): (1) Use equal parts of soft soap isopropyl alcohol and benzyl benzoate. (2) Warm bath rub with soft soap rinse. (3) While wet, brush over whole body benzyl benzoate mixture fo 5 min tes. (4) Let thi dry then paint it on again for 5 minutes. (5) Let this dry then put on same old clothes. (6) After 24 hours take cleansing bath and don fresh clothing Like myself Mallen (BMJ 2: 452, 1942) prefers the aqueous emulsion. Graham (BMJ 1: 412, 1943) obtained 99% cures in 1,000 cases treated with a single application without disinfecting clothing. Geffen (BMJ 2: 825, 1944) dispensed with both preliminary bath and scrubbing and attributed recurrences mainly to reinfection. Aq a bentonite was the vehicle and 2% Duponol C the emulsifier for the 25% benzyl benzoate preparation highly recommended by Slepyan (J 124: 1127 1944) Dermatitis venenata may follow benzyl benzoate and is sometimes severe (Daughtry: J 127: 88, 1945)

NBIN is applied as a spray benzyl benzoate 10 DDT 1, benzocaine 2, Tween 80 (wetting agent) 2, water to 100. Topicide is Lilly s proprietary of approximately this excellent formula. See Carpenter (JID 7: 93, 1946)

See Goldman (ADS 33 878, 1920) King (BMJ 2 416, 1940) I gram (BJD 54: 228, 1942) Robinson and Robinson (SouthMJ 40 1010, 1947) Tyrocaine, benzyl benzoate, benzocaine and tyrothrycin; Appel (NEngJM 242 74, 1950) benzyl benzoate especially effective if applied by medical personnel.

Derris (Rotenone) Treatment (Saunders: BMJ 1 624 1941; 1: 127 1942): (1) Use 4 ounces of powdered derris root in 1 gallon of water (2) To cupful of (1) add a dram of soap flakes; apply ove whole body 6 times in 2 days. One may dilute this to half strength to avoid rritation. Good when water is scarce, nonodorous nongreasy no sterilization of clothing no supervision needed, cheap, requires no skill to dispense. Epstein (ADS 45: 950 1942) reported 15% failures.

Eurax (containing 10% of crotonyl N-ethyl-O-toluidine) is reported as satisfactory (Couperus JID 13: 35, 1949; Tronstein OhioSMJ 45: 859 1949; Patterson: SouthMJ 43: 449 1950) Colorless, odorless and onstaini g it is a good ant pruritic according t reports.

Hexachlorocyclohexane, the gamma isomer 1% in cold cream, wa successful in 95% of the cases of Woolridge (JID 10: 363, 1948) The course of treatment consisted in a bath, inunction, 12-hour int rval, inunction, 12-hour interval, final bath. This is available as Kwell (Commercial Solvents Corp.) Cannon and McRae (J 138: 557 1948) cured 100 cases without irritation. Absorption of large amounts of the drug causes convulsive death (Mebbs J 138: 1.53, 1948) Experience has indicated that, as used in human scabies, it i effectual and harmless (Kornblee a d Combes: ADS 61: 407 1950; H lpern et al. ADS 62 648, 1950) Gamergent contained this along with other pesticidal chemicals effecti e against lice and other arthropods (Cornbleet et al.: ADS 66: 103, 1952) See Council on Pharmacy (J 144: 543, 1950)

Tetra Ethyl Thiuram Monosulfide (Tetmosol)—In 25% concentration in an alcoholic vehicle, then diluted 1 4 in water immediat ly prior to use, this drug seemed nonirritating cheap and effective on being rubbed over the body ccording to Percival (BMJ 2: 451, 194_, see Bradshaw Lancet : 273, 1944) Gordon et l. (BMJ 1: 803, 1944) recommended a soap containing Tetmosol, and an epidemic was controlled with a 10% soap preparation by Mell shy (BMJ 1: 38, 1945)

Pyrethrum.—An ointment containing 0.75% pyrethrins seldom irritates, has a pleasant odor and is generally curative when used daily for from 5 to 7 days, being applied each time after a hot bath (Sw itz r and Tedder: MinnMed 18: 793, 1935)

Thiosulfate—Hydrochloric Acid (Demyanovich's method: J 11 ; 2375, 1930; 1 31: 879 1944): (1) Shower bath with green soap and brush, during which clothing is disinfected. ( ) Rub onto skin for 15 minutes a 40% solution of thiosulfate. Dry with crystals of the salt. Rub on 5% solution of hydrochloric acid. (3) Repeat ( ). Cures 80% in 1 treatment of less than * hours. See Ravaut and Mahleu (BullsocfrancD 41: 135 1934); Kulchar and Meininger (ADS 34: 18 1936)

Scabicide was a propri tary supplying the Danl h treatment. It contained sulfur 10% balsam of Peru % and phenol 1% in a cold cream vehicle (Norris: OhioMJ 39: 551 194). Using the Danish method, Greenwood and Reilly (ADS 35: 602, 1937) reported over 5% of the patients were irritated although some 94% of over 4,500 patients were cured by a single application

See Oppenheim and Fantl (Kli Wchn 49: 187 1936) dermatitis from scabicidal medication, including death from ulfur past ; Montgomery (AnnMilitet 9: 219 1937) history description, bibliography Mellanby et al. (BMJ 2: 1 1943) treatment with various medicines Oppenheim and Smith (AIDS 46, 370, 1913) self 25 potassium carbonat 19 petrolatum 125 MacCormac (Practitioner 152 91 1944) enereal origin in Army; Dujardin (be IJD 68 73 1948) monographic Friedman (The Story of Scabies, Froben Press, 1919); Daly (JID 12 11 1949) new synthetic chemicals promising; Frakken and Van Vloten (be NTID 1949 p 311) pa i e tra fer of reactivity t parasite Grummitt (Sci 111: 361, 1950) di (p-halophenyl) alkyl carbi is highly toxic t mites, highly specific.

TYROGLYPHID MITES

Tyroglyphid mites, world wide in distribution are sometimes present in flour sugar ham meats, grain in mills, cereal foods, hair upholstery mattresses, etc., according to Anderson and Fishman (ADS 57 227 1948). *Aleurobius farinae* (Linn) has caused severe itching in handlers of wheat *Carpoglyphus passularum* (Hering) spoiled dates and prunes; *Glyciphagus domesticus* (deGeer) has been identified attacking grocers *Rhizoglyphus parasiticus* (Dalgetty) was found causing dermatitis about the toes and ankles of Indian tea plantation workers.

Tyroglyphus longior has caused in handlers of copra and cheeses an irritation which resembled scabies or dermatitis venenata (Cleveland ADS 41 831 1940 Thomas BJD 54 313 1942 Castellani BJD 25 19 1913 Saunders ADS 50 245 1944). Diffuse erythema without the suggestion of individual bites was observed by Nixon (BJD 56: 235 1944) whose patients, handling cheese cargoes at Glasgow were irritated by dead mites as well as by live ones. The cheese dust produced by their activity proved to be a sensitizer on patch testing. Dowling and Thomas (BMJ 2 543 1949) considered the powdery dust a primary irritant among the girls handling cheeses whom they studied. The hands arms, legs and sometimes the trunk may be involved but the face is seldom if ever affected. The lesions may be pruriginous papules which subsequently become papulopustules and pustules. The eruption seldom disappears spontaneously while the patient continues handling infested materials. Castellani found 5 to 10% betanaphthol ointment a useful remedy

T siro (Linn. 1758) in ha dlers of infested or m ty shells of vanilla, caused acarian cutaneous anillism to be di ti guished from chemical vanillism or intoxication.

De m toph goide scheremetewsi has been foun l in the urine but it pathogenicity is dubious (G rges UCutRe 4 820 1938). See Fisher et al. (ADS 63: 336, 1951) cutaneous infestation

Rhyzoglyphus hyacinth caused dermatitis from the handli g of decaying onions. Pruriginou inflammat on w th p h ad-sized papules, excoriat on and secondary infection, resulted from the act vity of the acari, which were present in large numbers on the plants. Pawlo ky an l Ste (ArDuS 158 443 1929) described their investigations of this onion mite dermat ti

Histiogaster entomophagus (Laboulbene 1852) swarmed in a tumor of a finger. It may also cause d sease imilar to cutaneou va illism due to *Tyroglyphus siro*.

Carpoglyphus passula um ha bee observed by Oliver and later by O Donovan (BJD 52: 297 1940) in et ologic relation hip with papular dermatitis of the forearms in laborers working with plums and figs.

FOLLICLE MITES

Demodicidosis.—*Demodex folliculorum* var *hominis* is a minute parasite occurring in the hair follicles and sebaceous secretion in a considerable proportion of adults. The animal is cigar-shaped, measuring about 0.3 by 0.04 mm. Some believe it causative of some cases of rosacea, for in cases in which the



Fig 325.—*Demodex folliculorum* in sebum. (Dr Eugene A. Hand.)





Fig. 326.—*Demodex folliculorum*. (Drs. Ayres, Anderson and Foster.)

Fig. 327.—Canine demodicidosis (sarcoptic mange). Inflammatory and foreign body reaction to acarines in canine skin. (Maier JLabClinM 24 594, 1939.)

organisms are numerous, clinical improvement along with their disappearance is obtained with sulfur ointment (Ayres: ADS 21 19 1930). Others have accredited it with the causation of tinea versicolor like discoloration of the skin and tinea-like impetiginoid, and rosacea like lesions (Miskjian ADS 43 745 1941 Nicholas ADS 47 793 1943)

See Whitfield (ProcRoySocM 13: 102, 1920) organisms found in resistant case of scabby dermatitis of face thought contracted from mangy dog, cured with sulfur ointment, Lawrence and Brodie (MJAustral 1: 520 1931) in blotchy dermatosis of face, "pityriasis folliculorum" Fuss (AnnderD 4 1083, 1933; 6: 326, 1933) action perhaps foreign body in sebum, photomicrographs; Lawrence (ADS 32: 633, 1935) in impetiginous lesions of face absent elsewhere; Henry and Hory (Ibid 193, p. 198) pathogenicity dubious, histology of canine disease Batunin and Iolkin (DWchn 101: 1355 1935) frequent in rosacea, infrequent in normal Maier (JLCM 21 594 1939) in dog Miskjian (ADS 63: 28, 1951) tiny red papules in scalp perhaps caused by Demodex.

RAT AND BIRD MITES

Parasitoidea is the superfamily containing *Liponyssus bacoti* the common rat mite and *Dermanyssus gallinae* a common parasite of fowls which may temporarily infest human beings.

Rat mites transmit rickettsialpox (q v) When efforts are made to exterminate rats, *L bacoti* seek other blood producing in human beings itchy wheals and papules with central puncta especially on the extremities. Insecticidal spray or fumigation with HCN will exterminate them The rash may be

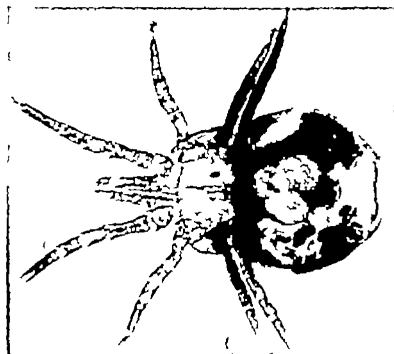


Fig 416.—*Dermanyssus gallinae* (Dr Joseph W. Shaw and M H A Pommerening ADS 61 466, 1950.)

mistaken for scabies. Department store employees were the sufferers observed by Weber (J 114 1442, 1940) and relief followed the extermination of rats, during which procedure an insecticidal spray should also be used to prevent human invasion when the rats are killed (Lowell ADS 54 278 1946) The organisms are tiny red mites about 0 5 mm across and 0 75 mm. long

Fowl mite infestation results from the nocturnal activity of the animals, which migrate from abandoned nests of pigeon, starling or sparrow as a rule *D gallinae* is pear-shaped about 1 0 mm over-all grayish yellow and eyeless, able to run swiftly over the skin into which it does not burrow Infestation may be mistaken for delusion of parasitism It is a cause of lichen urticatus (Rockwell ADS 68 82 1953) The mites may reach a sleeping patient by way of an open window seeking blood on which to feed when the avian hosts *have departed from their infested nests. They may reach the* patient directly too in the course of handling chickens or pigeons or cleaning the coops. A pet canary was the source in the case of Cole and Driver (ADS 37 322, 1938)

The bites in man occur especially on the upper trunk, pubes, breasts, umbilicus, face and scalp and are urticarial and itchy The disease once

recognized, is easy to manage by destroying the source and by using repellents, such as Kwell on the patient and a suitable spray along the path of the migration.

See Rickettsialpox; also Toomey (UCutRev 25: 705, 1931) gamasoidosis Lawrence (MJAustral 2 410 1931 2 16, 1935 BMJ 2 572, 1935), D. [illegible] Sulzberger and Kaminstein (ADS 33 60, 1936) D. [illegible]; Boyt (BJD 49 65, 1937) D. [illegible], Riley (MinnM 23 422, 1940) L. baceti Anderson (ADS 50 90, 1944) life history of L. baceti and case resembling scabies; Rothman and Niederman (ADS 55 128, 1947) L. sp in Chicago Reeves et al. (Sci 105: 411, 1947) L. [illegible] [illegible] contained [illegible] of western equine encephalomyelitis Shaw and Pommerenk [illegible] (ADS 61 466, 1950) D. [illegible] Pirila and Kilpio (ActaD-V 29: 70, 1949) rat mite dermatitis.

CHIGGER MITES AND GRAIN ITCH

Tarsonemoidea (Grain Mites) —These mites are predaceous on insects which attack grain crops. *Pediculoides ventricosus* lives as a parasite especially on the larvae and nymphs of the corn moth. When it is unable to attack these insects, it passes onto the body of man and produces a polymorphous, papular or papulovesicular erythema, accompanied by severe itching and sometimes by fever

In Indiana the principal insect hosts of *Pyemotes (Pediculoides) ventricosus* are the Angoumois grain moth and the wheat jointworm, the latter being the larva of a small fly that lays eggs in the wheat stalks, which are not destroyed by the high-cutting combine harvester machines; the storage of surplus corn has encouraged the luxuriation of the grain moth (Booth and Jones J 150: 1575, 1932) Male and female mites are sexually mature at birth. The males, relatively few and usually among the first born, remain on the mother's abdomen and fertilize females as they are born, soon after which the females scatter in search of food. They can travel only short distances and cannot long survive especially in warm weather without food. Under favorable conditions new litters appear at intervals of about 1 week and as many as 300 young are produced each time.

The parasites attack people working with grain, particularly those who unload it (Rogers: J 123: 887 1943) Synonymy of such names as prairie itch and Ohio scratches was reviewed by Kittredge (VaMMonth 60: 357 1933; J 107: 2109 1936) The first American description of the cases was that of Rawles (IndianaMJ [illegible]: 837 1909) Occurrence in Italy was noted by Ancona (Policlinico 30 45 1923) who observed that exposed mill workers after a time developed asthma as a result of infestation. Australian incidence was described by Swan (MJAustral 2: 573, 1934)

Leptus autumnalis was identified attacking persons engaged in picking bush beans in the vicinity of Basel, Switzerland, by Schuppli (SchweizMWchr [illegible] 368, 194[illegible]) They have been found in Great Britain France, Holland, Germany and Denmark (v Mallinckrodt Haupt: UCutRev 34 744, 1930) Palestine cases were reported by Katzenellenbogen (ADS 55: 631 1947)

Trombidoidea (Chigger Mites and Harvest Mites) contains the family Trombidiidae which are of medical interest These are acari of silky hairiness, reddish in color free and predatory as adults, as larvae parasitic on vertebrates and arthropods. The larvae known as *Leptus*, or harvest mites, are fixed for various periods of time on animals whose blood or lymph they suck. All larval trombidiidae attacking man produce local phenomena and sometimes general intoxication, with erythema of severity which varies with the species and number of parasites. These tiny animals are common in the temperate zones, and their attacks usually are credited to the much rarer chigoe, a flea. Only the larvae are parasitic. On contact with the vegetation on which these are located the skin is invaded. They run at the rate of 10 cm. per minute and tend to attach themselves on thin epidermis where they happen to meet an obstruction such as a garter belt or brassière. They do not burrow Within a few hours they are engorged with blood and drop off (J 117 406 1941) See Wharton and Fuller (Manual of the Chiggers U.S. Nat'l Museum, Washington 1952)

Trombicula irritans (Riley 1873) is the chigger common in America. It is brick red in color and oval in shape and it measures from 0.3 to 0.5 mm. by 0.25 to 0.3 mm. It lives in nature on woody decaying substances and the fecal matter of arthropods and occurs during July and August in enormous numbers in grass and bushes, fields, and moist, swampy places.

Trombicula species transmit Japanese river fever (scrub typhus; see p. 257)

Neoschoengastia nuneri infestation, observed by Andrade (BolMédHospInf, 1944; GacMédMéx 77 221 1947) in the vicinity of Mexico City, resulted in disease resembling grain itch with pruritic lesions, insomnia, fever leukocytosis and eosinophilia.

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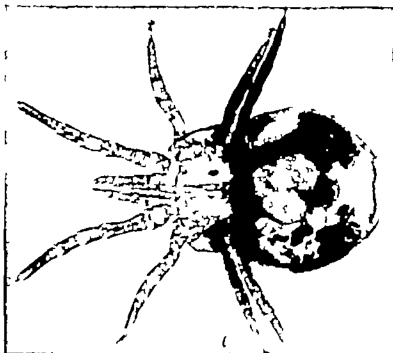


Fig. 836.—*Dermanyssus gallinae* (Dr Joseph W. Shaw and M R. A. Pommerening ADS 61 466, 1950.)

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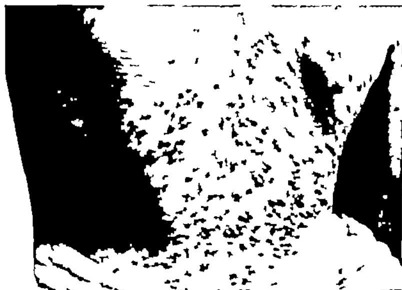


Fig. 829.—Grain itch. (Dr J F Schamberg.)





Figs 830 and 831.—Trombidiosis (chigger bites): hemorrhagic, excoriated lesion on the thorax and abdomen. Vesiculation and fever may be present. Hemorrhagic lesions of leg are 6 days old. (Dr Howard J Parkhurst.)

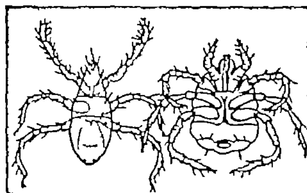


Fig. 312.—*Trombicula irritans* male and female larva (×100) (Dr C. V. Riley)



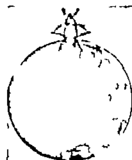


Fig. 313.—*Pediculoides ventricosus* male (After Braun)
Fig. 314.—*Pediculoides ventricosus*, gravid female. (After Webster)



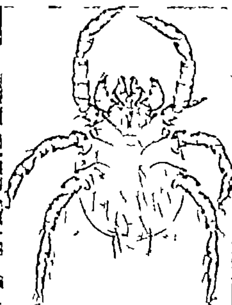
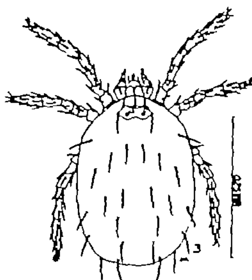


Fig. 315.—Section from chigger bite on leg, 4 days old, showing vascular engorgement in the subcutis, lymphocytic perivascular infiltration and edema. (Dr H. J. Parkhurst.)

Fig. 316.—The common North American chigger *Trombicula irritans* (Riley). A specimen from Dr H. L. Ewing collection, approximately ×40. (Dr H. J. Parkhurst)

Figs. 537 and 538.—*Infestation resembling grain itch caused by* [illegible] (× 8) (Dr. Robert N. Andrade.)





Figs. 539 and 540.—[illegible] (× 8) (Dr. Anna Hoffmann and Robert N. Andrade.)

Harvest mites are abundant during the summer and autumn in some countries. The larvae attack the legs and accumulate in the regions of bands which bar their movement such as belts and girdles. They force their rostrum into the skin provoking severe itching and papules surrounded by red or violaceous areolae. These are soon excoriated. Intoxication and fever may result. The acari live only a few days on man. The eruption produced by *P. ventricosus* is fairly well generalized and rapid in development. Schamberg (JCutDis 28 67 1910) described 3 clinical types: urticarial vesicular pustular, the most common, varicelloid and erythema multiforme like. Itching has its onset after perhaps 24 hours. It is almost intolerable and is worse at night. Secondary infection is quite common as a result of abrasion. There may be malaise, some fever and moderate lymphadenitis. Urticaria is differentiated by the presence in grain itch of central vesicopustules. Varicella is less pruriginous, and the course of its eruption is more rapid. The lesions of scabies are different in character and distribution.

Treatment.—One should avoid exposure to the animals. Weak parasiticidal ointments to which an antipruritic such as 0.5 to 1.0% phenol has been added, prove comforting. Some harvest workers claim that they avoid infestation by taking sulfur by mouth. Immunity occurs in some persons and mites are partial to others. Bathing with soap, applying to the skin a weak dilution of phenol in boric acid ointment and dusting the clothing with sulfur are procedures which yield some protection (Parkhurst ADS 35 1011, 1937). Carbon tetrachloride, collodion or nail polish, applied to the bites, is comforting. Careful but firm wiping of lesions with gasoline gives relief for a few hours (Fasting J 119 536 1942). Collodion with Metaphen relieves the itching of a lesion to which it is applied (PHRpts 55: 1312, 1940). Ethyl aminobenzoate, 15% in flexible collodion is likewise comforting but occasionally imprisons pathogenic cocci, which then produce an impetiginous bleb at the site (Sutton J 120 26 1942). During the period of illness and intoxication, cortisone in full dosage by mouth gives immediate and great relief. The antihistamine compounds are less effective.

Various repellents successfully prevent infestation, among the best of which are 6-12 and Kwell the active ingredient of which is hexachlorocyclohexane. A lotion containing 2% rotenone is helpful (Williams et al. SM&SJ 103 199 1941). A solution of 5% dimethylphthalate and 2% soap is useful for dipping clothing so as to render it repellent (J 144 1324 1950). Disinfestation of terrain may be achieved by spraying on the ground the insecticide Dieldrin at the rate of 2¼ lb. to the acre and this is also apparently useful against ticks (Traub et al. JEconEntomol 47 429 1954 quoted by QMN J 157 1172, 1955). The Army clothing impregnant M 1960 protects against chiggers and ticks. It contains equal parts of N butylacetanilide, 2 butyl-2-ethyl-1 3-propanediol and benzyl benzoate with 10% of an emulsifying agent.

Tetranychinae, spider mites, spinning mites, or red spiders, are tiny acarine animals which feed on the tender tissues of plants. *Tetranychus molestissimus* is found in Argentina and Uruguay where it is known as the Bicho colorado, and where it attacks mammals and man, causing severe itching and in the latter fever as well.

Tetranychus telarius is a species parasitizing vineyards, causing the red disease. The bite in man provokes a tiny blanched papule that lasts a few minutes (Brumpt, 1940).

CREEPING ERUPTION due to a similar mite was reported by Murray (BMJ 1: 1076 1930) the disease being common in Natal and Zululand. The lesions are characteristically thin, inflammatory tracts, which lengthen. The feet, genitalia and buttocks, of natives and Europeans of any age, are attacked by predilection especially in the hot wet months. The superficial burrow is actually about 0.33 mm. wide, seemingly wide because it is surrounded by inflammation, and it is commonly secondarily infected. See p. 633.

HEXAPODA

In true insects, the adult possesses a single pair of antennae and 3 pairs of legs. The body is segmented and divided into head, thorax and abdomen. Typically the thorax consists of 3 segments and supports 3 pairs of legs and

2 pairs of wings and the abdomen is composed of 10 segments, the terminal one modified for sexual purposes. Some insects develop without metamorphosis, the adult developing from the nymph which hatches from the egg. Others undergo gradual, others, partial and still others complete metamorphosis in which the adult evolves from the pupa which has developed through several larval stages from the egg.

Insects perform their pathogenic services to mankind by mechanical and chemical external irritation, by insertion of venom, by provocation of eczematous and systemic allergy, by evolution and migration on, in or under the skin, and by transmitting, inoculating and disseminating viruses, bacteria, fungi, protozoa, filariae and other parasites (Jarcho, WarM 3: 447, 596, 1943).

See Fox (Insects and Diseases of Man, Blakiston, 1925); Hull (Diseases Transmitted from Animal to Man, Thomas, 1930); Huff (Sci 74, 456, 1931) types of transmission of disease from arthropod to man: biologic cyclopropagati e cyclodevelopmental and propagati e, mechanical; Riley and Johannsen (Medical Entomology, McGraw Hill, 1932); Neveu-Lemaire (Traité d'entomologie médicale et vétérinaire, Vigot, 1938); Sutton and Sutton (Diseases of the Skin, Mosby, 1939, p. 1331 ff.); Belding (Textbook of Clinical Parasitology, Appleton-Century, 194_, p. 589 ff.); Smart (Handbook for the Identification of Insects of Medical Importance, British Museum, 1943, 269 pp.) including fleas and arachnids, practical and authoritati with key; Obermayer (J I I 3: 454, 1942) tropical dermatoses and entomology; Brumpt (Précis de Parasitologie, Masson, 1949, p. 1667); Herms (Medical Entomology, Macmillan, 1950) authoritati guide in human and veterinary science; Craig and Faust (Clinical Parasitology, Lea & Febiger, 1951, p. 628, classification, p. 633, medical importance); Roy and Brown (Entomology, Medical and Veterinary Including Insecticides and Insect and Rat Control, Calcutta, 1954).

Hexapodan Dermatoses include those due to the following orders

Orthoptera	grasshoppers, crickets, cockroaches
Ephemerida	may flies, lake flies
Trichoptera	caddis flies
Mallophaga	biting lice of birds and mammals
Anoplura	sucking lice, pediculi
Heteroptera	bedbugs, assassin bugs, kissing bugs
Siphonaptera	fleas
Coleoptera	beetles
Lepidoptera	moths and butterflies
Diptera	two-winged flies, mosquitoes, botflies, houseflies
Hymenoptera	bees, hornets, wasps, ants, ichneumon flies

Orthoptera.—These are of little dermatologic significance. The order includes grasshoppers, crickets, cockroaches and the like; they have chewing mouth parts and two pairs of wings, of which the outer is more or less parchmentlike and the inner membranous and folded when at rest. Roaches and crickets are dermatologically insignificant, although they are capable of serving as mechanical vectors of pathogenic bacteria.

Zonocerus elegans(?) — *Eupelopus dure di*, an African wingless locust, discharges a yellowish fluid from the pores at the side of the body which may produce dermatitis venenata with swelling, redness and vesiculation (Stannus, quoted by Riley and Johannsen, 1932, p. 118). Hjalmar Carlson described to me his experience during plagues in Kansas; mechanical damage resulted from the forceful removal of grasshoppers which were clinging to the skin and the lesions burned and stung and required several days to heal.

Ephemerida.—The order includes May flies, which may appear seasonally, particularly in the Great Lakes region, in pestilential myriads, so that a lake shore may be heaped inches deep with the putrescent remains. Inhalation of their fragments may cause asthma, sometimes urticaria. Rarely the insect crushed on the skin provokes eczematous dermatitis (Figley, JAllergy 11: 376, 1940).

Trichoptera.—The caddis flies appear in enormous numbers about lakes and streams. They occasionally cause asthma and urticaria (Parlato, JAllergy 3: 1?0, 459, 1932).

Mallophaga.—The biting bird lice are wingless forms which attack birds and animals. Members of the genera *Goniocotes*, *Lipeurus*, *Goniodes* and *Menopon*, according to Toomey (UCutRev 25: 705, 1921), particularly attack cleaners of fowl coops and handlers of chickens and pigeons. Biting lice are vectors of *Dipylidium caninum*, the dog tapeworm, which infests dogs, cats, and rarely human beings.

PEDICULOSIS

Anoplura.—These wingless sucking lice parasitize warm-blooded animals. Only the family Pediculidae are hominixenous. Pediculi of man, exclusively hematophagic insects, are specific parasites. Their voracity is considerable, and they eat 2 or 3 times a day. They have little resistance to inanition and die in discarded clothing in a few days (Davidson, MJAustral 1: 533, 1943), more quickly when humidity is low. The bite is

disagreeable and itchy in persons who are not accustomed to it or who possess special sensitivity Lice are permanent parasites. Seasons have no influence on their generations, which succeed one another without interruption. The life span of adults is perhaps 6 or 8 weeks. The resistance of the lice and their eggs to heat is relatively slight. In delousing, the procedure must be conducted with care so that all parts of the clothing and coverings are exposed to adequate heat and drying

Pediculus humanus capitis and *P humanus corporis* interbreed without reduction of fertility their biologic characters are intergradient (Nuttall: Parasit 11 329 1919 Keilin and Nuttall: Parasit 22 1 1930)

The head louse is grayish in color The male is some 1 6 mm. long and 0 7 mm wide, the female is 2.7 mm by 1 mm. It lives in the hair of the scalp occasionally in the beard. Rarely it is found in the pubic region. The female fixes her eggs or nits to the base of the hair The young hatch on the sixth day and become adults on the eighteenth, after having undergone 3 moults. Eggs may then be laid within a day or two

The body louse is larger than the head louse and is dirty white in color The male measures 3 mm. in length and 1 mm. in width the female is 3.3 mm by 1.15 mm. This louse is found on the skin only at the time of feeding Ordinarily it hides in clothing or ornaments. It is cosmopolitan. It is a dangerous vector of typhus fever While the exact method of transmission of this disease is not known the excreta of the infected louse may be infectious. The spirochete, *Borrelia recurrentis* of relapsing fever is transmitted from man to man by the body louse. See Buxton (BMJ 2 1245 1939 1 341, 1940 The Louse Arnold, 1947) Bacot (BMJ 1 788 1916) entomology

Phthirus inguinalis (Phthirus pubis) Forelegs delicate, with long slender claws other legs stout, with short, stout claws thumblike process of tibia short and stout abdomen short and broad. Nits are fixed at the base of hairs. Young hatch on seventh day and are able to reproduce 15 days after their appearance. The pubic louse is not known to transmit infection.

Pediculosis Corporis.—As a rule the animal resides in, and lays eggs near the seams of the clothing. It comes upon the body only to feed, commonly in the interscapular shoulder and waist regions. Early lesions are minute, red noninflammatory points, elevated but little Usually the lesions quickly become papular and wheuled. Excoriation leads to the appearance of bloody crusts. Itching is a prominent symptom Secondary infectious manifestations frequently develop Acquired hypersensitivity to lice may result in urticaria (Peacock Nature 118 696 1926) In long-standing cases there may be more or less brownish pigmentation. Parallel linear excoriations in the interscapular region are almost pathognomonic. Among British troops in 1916 95% of the men were infested and they supported from 10 to 20 and even up to 1 000 cooties (Peacock BMJ 1 745 784, 1916)

EXPERIMENTALLY lice caused at first only pin-point, flat, red, noninflammatory lesions but, after a week and as a result of developing sensitivity reaction became papular with surrounding erythema, and even vesicular reported Peck et al. (J 123: 821 1943) Intradermal tests with louse antigen, that from feces being especially active caused transient wheals in nonsensitive but tuberculoid reactions in sensitized individuals. The distress, widespread dermatitis, and psychic disturbance of the host were described by Rosebase (NEngJM 234: 665, 1946) Morris (NEngJM 233: 180 1945) attributed leg ulcers, in some instances, to infestation. The rearing of a colony of lice was described by Culpepper (AmJTropM 24: 327 1944) Lice nurtured upon a laboratory worker depleted the blood at the rate of from 10 to 25 cc. daily causing anemia (Finkel: Arch f rI ereM 1934, p. 34)

MORBUS ERRONUM (VAGABOND'S DISEASE)—Persons long infested develop pigmentation from chronic dermatitis, excoriation and perhaps malnutrition. The pigmentary chronic dermatitis occurs in grossly neglected and subnormal, vagrant individuals. Animals on deficient diets become susceptible to pediculosis (Y dkin: J 101: 921, 1933) and the lack of the B complex is significant perhaps, in human infestation (György: ProcSoc ExpBiol 33: 383 1935)

TREATMENT.—The clothing must be sterilized. It may be autoclaved, ironed with a hot iron dipped in naphtha or gasoline, or boiled. It may be fumigated with hydrocyanic acid, carbon tetrachloride or 10% creolin solution. To discard and dry the clothing for several days suffices by starving the



Fig. 341.—Pediculosis corporis.



Fig. 342.—Head louse nd nits on hai (Dr. O. G. Costa.)



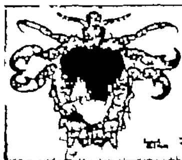




Fig. 343.—*Pediculi humanus orporis* (Dr. Fred Weidman.)
Fig. 344.—*Phth p bis.* (Dr. Fred Weidman.)
Fig. 345.—N t of louse ttached t hai

lice and desiccating the nits. Fumigation with methyl allyl chloride is effective (David BMJ 2 108 1943) Resistance to DDT develops, and lice have been reared through their complete life cycle on cloth impregnated with 0.1% DDT in acetone (Hurlbut et al Sci 115 11 1952)

Skin irritation and secondary infection may necessitate astringent baths, such as weak potassium permanganate In cases complicated with ecthyma and furunculosis nits are usually present in the pubic, axillary or perineal hair crop the hair change the kit and remove nits with the application of paraffin, and relief may be obtained (Semon and Barber BJD 29 173 1917)

Pediculosis Capitis.—Children are more susceptible than adults. Itching is usually the predominant symptom The presence of parasites and their ova is discoverable on close examination. Usually one finds exudative coccic dermatitis of variable severity matting of the hair especially in the occiput, and lymphadenitis, especially of the posterior cervical nodes. Conjunctivitis was often present, and corneal ulcer was not rare in the cases of Hirtenstein (BMJ 2: 75 1943)

DIAGNOSIS is simple if the disease is suspected. The animals are active and visible, and nits are readily found if sought. They show white fluorescence under Wood's light, which aids in rapid diagnosis (Spiller ADS 63: 499 1951)

TREATMENT.—Clipping the hair is seldom necessary, although it facilitates the work One application of Topicide will probably cure A simple method of therapy uses the petroleum cap the scalp is soaked with a mixture of equal parts of coal oil and olive oil (inflammable) then loosely bandaged After 12 to 24 hours, the dressing is removed, and the head scrubbed with soap and water Larkspur is satisfactorily employed in the same way Way used 20 cc. of xylol in 30 Gm. of petrolatum. Tincture of cocculus indicus, 33% in water may be applied freely 2 or 3 times daily for several days, its use supplemented by frequent shampoos. Persistent nits may be loosened with weak washes of acetic acid (vinegar) or lemon juice and removed with a fine-toothed comb DDT 2% emulsion, 1 application without previous washing is fairly reliable (Frazer BMJ 2: 263 1946) but the animals die slowly are irritated and wander from the scalp disgustingly when attacked with DDT alone A dust containing 10% DDT and 90% pyrophyllite was effective (Cowan et al. AmJTropM 27 67 1947) who applied about a teaspoonful to the scalp and left it without washing for one week the course might require repetition. Rotenone powder alone does the job (Murphy SouthMJ 36 53 1943) Davis (J 123: 825 1943) reported single application cures with phenyl or benzyl cellosolve 40% ethanol 30 methyl salicylate 5 and water to 100 NBIN containing benzyl benzoate 68 Tween 80 14 parts, ethyl aminobenzoate 12, and DDT 6 to be diluted with water to 1/6 this strength is efficient for both lice and scabies (Eddy: JID 7 85 1946, Am JHyg 47 29 1948) Delousing of 1,500 000 persons in 45 days was achieved by dusting their underclothing with DDT 10% in pyrophyllite with Flit guns (Ahnfeldt JTennMA 37 263 1944) A second powdering a week after the first kills what hatches later Kwell containing hexachlorocyclohexane may be recommended highly Lethane (n butyl-carbitol thiocyanate) 15% in purified kerosene a single application left in the uncovered scalp for 2 or 3 days, kills the lice effectually (MacHaffie CanadPubHealthJ 32: 606 1941) A benzyl benzoate preparation was approved by Blackstock (BMJ 1 114 1944) A thiocyanoacetate and sulfosuccinate preparation was effectual and rarely irritating according to Shelanski et al. (ADS 51 170 1945) The agents recommended by Busvine and Buxton (BMJ 1 464 1942) were (1) 25% technical lauryl thiocyanate in white oil (2) 50% lethane 384 in white oil and (3) derris cream.

Sources of reinfection should be controlled for a high proportion of the patient's contacts also harbor lice Superstitious Polish refugees in England during World War II would reinoculate their children with lice as fast as they were deloused on the hypothesis that it was unhealthy not to be infected.



Fig. 846.—Pediculosis capitis, showing ova on hairs. (Dr J. L. Lak)

Fig. 847.—Pediculosis capitis with secondary infectious eczematoid dermatitis. (Dr O O Costa)

Phthiriasis.—Ordinarily the crab louse confines its activities to genital, abdominal and anterior thoracic regions, but it may involve the axillae, eyebrows, lashes and body hair of hirsute persons. Recognition depends on discovery of the active, tiny reddish brown animals, or their ova attached to hairs, or the iron rust like spots of excrement. Cutaneous lesions and symptoms are like those occurring in pediculosis corporis. Infection can readily occur through contact with contaminated bedding and clothing as well as by intimate contact. The animal lives on the skin, not in the clothing.

It is not especially unusual to find the lice and nits on the eyelashes, and this region alone may be involved (Wright and Friedman AOphth 11 995 1934 Fleming BMJ 2 87 1943; Goldman ADS 57 274, 1948) I saw a case of heavy infestation of the scalp with *P pubis* in a child, asymptomatic and sought because the taches bleuâtres were recognized on the extremities.

A remarkable case of bullous allergic reaction to the presence of the animals was reported by Kern et al. (ADS 65 334, 1952) which actually resembled pemphigus.

Maculae Caeruleae (taches bleuâtres) are rounded slaty gray or bluish macules, sharply discrete and of pea to fingernail size occasionally seen on the thighs, abdomen and thorax of heavily infested persons. They are due to introduction into the skin of salivary gland material of the lice and disappear after disinfection (Dugué and Mallet abs JCutVD 1: 319 1883) Fever and malaise as well as this curious vasomotor phenomenon are sometimes observed (Saidi and Farrington AmJMedSci 214: 308, 1947)

Treatment —DDT 0.5% in cold cream, a single application to hairy parts below the neck is simple and effective (Sutton, Jr BullUSAMD 4 45 1945) Kwell, containing hexachlorocyclohexane, may be recommended. Using these agents, it is unnecessary to clip the hair or to shave the parts. Insecticidal treatment must be coextensive with the parasitism. Tincture of cocculus indicus, diluted with 3 parts of alcohol or water may be applied several times daily Camphor 1% in mineral oil, is excellent. Mercury ointment is less satisfactory When the eyelashes are involved, the patient is usually a child, but a general anesthetic is seldom needed to permit manual removal of the insects and their ova (Ronchese NEngJM 249 897 1953)

BUG BITES

Hemiptera.—Members of the order have sucking mouth parts enclosed in a segmented beak, which arises from the front of the head; they are generally provided with 2 pairs of wings; they undergo incomplete metamorphosis. In the suborder, *Heteroptera* the anterior wings are partly formed into elytrons, while the posterior are membranous; only these are medically important. Bedbugs, squash bugs stink bugs and assassin bugs are familiar names of representatives. While many entomologic subdivisions of the order exist, the families Cimicidae (Bedbugs) and Triatomidae (Assassin Bugs) are of interest. Reduviid bugs, including the Triatomidae are blood suckers, capable of inflicting painful bites with local swelling or even generalized urticaria from the potent salivary toxin. The so called "kissing bug" accomplishes its bites without producing pain at the time (Arnold and Bell: HawaiiMJ 3: 121, 1944)

Assassin Bugs have a short, trisegmented beak attached to the tip of the elongated head, and a distinct neck; the antennae have 4 segments, the tarsi 3. Several thousand species are known. They are predaceous, living on the blood of insects. In man, their bites are decidedly painful, and productive of swelling and soreness which may last for a week. The bites of hematophagic species are much less consequential than those of the hunting types. Members of the genus *Triatoma*, in particular *T megista* (Burmeister, 1835) are vectors of *Trypanosoma cruzi* (American trypanosomiasis) Also are several species of other genera. Several species, including *Triatoma (P mstrongylus) megista*, can puncture the skin painlessly withdrawing blood from exposed tissues, such as the lips. Other families of Hemiptera contain members which can inflict injuries.

Notonectidae, or back swimmers, small aquatic bugs that swim on their backs, are able to inflict painful bites.

Belostomatidae contain various species of *Lethocerus* that bite painfully

A few of the plant feeding Hemiptera Heteroptera may suck the blood of man on occasion (Riley and Johannsen, 193_)

Bedbugs.—Cimicidae have vestigial hemelytra and no posterior wings antennae in 4 segments, lower lip in 3 segments, tarsus of 3 segments, no ocelli.

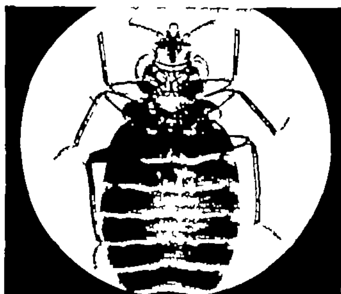


Fig. 848.—*Cimex lectularius*, the bedbug (×20). (From Gradwohl: Clinical Laboratory Methods and Diagnosis, Mosby.)





Fig. 849.—Bites on thigh and ankles produced by *Haematosiphon inodora* (Dugès, 1892). (Dr. Robert N. Andrade.)

Fig. 850.—*Haematosiphon inodora*. (Dr. Robert N. Andrade.)

The genus *Cimex* includes *C lectularius* (Merrett 1667) the common bedbug and other species which may attack man.

Cimex lectularius the bedbug is cosmopolitan. The adult is 4 to 5 mm. long by 3 mm. broad. The body is covered with short bristles and hairs Its stink glands lie on the inner surface of the mesosternum. Its eggs are pearly white oval, and about 1 mm. long and are laid intermittently over a long period in crevices of bed and furniture and under seams and loose wallpaper glued to the spot by a sort of mucilage. Adults have been kept in a closed vial for a year without food and have survived. They feed on other creatures if man is not available Three or 4 generations a year, in combination with their natural hardihood and inappetibility to birds and other predatory creatures, make them a pest hard to conquer

The bedbug makes cutaneous punctures in efforts to reach the capillaries, but it approaches the body only to feed, residing in crevices of mattresses and elsewhere A transitory wheal develops, and this may be succeeded by a circumscribed purpuric lesion which persists for several days. Erythematous wheals of uniform size about that of the fingernail three in a row with central red puncta are typical The lesions are usually multiple and give rise to more or less itching and burning The condition is to be differentiated from urticaria, in which the eruption is generalized and more or less symmetric and the lesions do not present central puncta. Itching and burning can be relieved by carbolized calamine lotion. The history is strongly suggestive when the patient retires without lesions and awakes with new ones.

The crevices of the seat covers of a particular trolley car harbored bedbugs which caused a puzzling epidemic of bullous erythema of the calves of the women who rode the vehicle (Kinnear Lancet 2 65 1948)

Bedbugs may be got rid of by (1) fumigation with HCN burning sulfur formaldehyde or other toxic vapors (2) heating the house to some 130 F by shutting the windows and turning up the furnace or (3) hanging coal tar naphtha on cotton diffusion screens near the walls for 24 hours at 60° C. Mercuric chloride solution may be poured in cracks where the eggs are (Cragg IndJMRes 11 449 1923) Beds and springs may be torch flamed Repapering, repairs of cracks, painting and DDT spraying are effective.

Hematosiphon inodora (Duges) a poultry bug prevalent in Mexico, spread from chicken houses to attack human beings, reported Andrade (MedMexico 31: 143, 1951) The bites appeared in small zigzag groups, evoking wheals, papules, vesicles, excoriation, insomnia and secondary infection. They were generally located on the legs, occasionally on the scalp. The bat bug has been known to bite human beings in Japan (Brumpt, 1949)

See Cummings and Austen (The Bedbug, Its Habits and Life History and How To Deal With It, British Museum, 1932); Ashmore and Hughes (BMJ 1 160 1938) coal tar naphtha technic Slack (Nature 143 78, 1939) 13 autosome pairs in *C lectularius* Windsor McLean (MJAustral 2 211 1939) *C hemiptera* among Chinese laborers in Nauru; Yasui (abs ADerm 46: 745, 1942) antigen and complement fixation tests Med. Research Council (BMJ 1 198, 1942) insecticides useful in bomb shelters pyrethrins, thiocyanate, and coal tar naphtha, with proper maintenance.

FLEA BITES AND CHIGOE INFESTATION

Siphonaptera (Fleas) are insects which parasitize mammals and birds. They are wingless, with highly chitinized and laterally compressed bodies. The legs are fitted for jumping. Mouth parts are formed for piercing and sucking Their parasitism is not closely limited the hungry flea is a desperate creature, and its willingness to exchange hosts is the basis of its danger as a carrier Their transmission of bubonic plague is notorious. *Xenopsylla cheopis* is the rat flea especially important as the vector of plague and endemic typhus. The flea infected with *P pestis* is not infectious until bacterial masses obstruct its esophagus, and the flea so infected excretes organisms in its feces and dies within 48 hours (Eskey: AmJPubH 28: 1305, 1938) Many other species bite man and may transmit disease.

The flea exposed to strong light seeks to hide and if kept for several days in a narrow glass vial gives up his proclivity for jumping these facts form the basis of his training for participation in a flea circus.

Siphonaptera comprise families **Pulicidae**, having well-developed thorax small head quadripartite labial palpes and an abdomen which even in the gravid female never becomes deformed; and **Sarcopsyllidae**, having short thorax, undivided labial palpes, and an abdomen which in the gravid female bulges considerably

Pulex irritans the common flea, is of practically universal distribution. Some individuals are apparently more susceptible than others to its attacks, and the severity of ensuing irritation is likewise variable depending apparently on acquired hypersensitivity (Boycott Nature 118 591 1926) Immunity eventually develops (Lunsford ADS 60 1184 1949) Desensitization with flea antigen may perhaps be successfully accomplished (Cheney et al. AmJ



Fig 551 —*Pulex irrit* , the flea commonly affecting human beings. (Gradwohl: Clinical Laboratory Methods and Diagnosis, Mosby)



Fig. 552.—Flea bites on ankles.

TropM 19 327 1939, Hatoff J 130 8[illegible]0 1946) Large doses of thiamin may prevent bites or diminish reaction to them (Eder APed 62 300 1945) Ordinarily the cutaneous lesion is a pale or erythematous, evanescent, itchy wheal, with a minute reddish, hemorrhagic point at the site of puncture. Occasionally the manifestations may simulate purpura. To diagnose one may don white hose, sit in the dark put on light suddenly and find the fleas on the socks (Baskin ADS 39 1075 1939) Camphor and essential oils gen-

erally exert a prophylactic effect in keeping the body free from the pests. Derris derivatives are valuable (One Spot Flea Powder) For the relief of the itching which in some instances is intense resort may be had to carbolized calamine lotion. Shaking out the bedding prevents the hatching of eggs. Where fleas are troublesome floors should be as bare as possible. Cedar oil and other oils used in floor cleaning will drive away fleas. DDT dusting and rodent extermination are control measures. Various repellents, such as Kwell are effective.

Syndrome of de Amicis.—In Naples was reported a mysterious form of prurigo affecting Americans visiting Italy It was manifested by the simultaneous occurrence in several members of the same family beginning at the time of the patients arrival, of an eruption made up of rose-colored papules covered by bloody crusts located on the trunk and the extremities. DeBlasio (BullsocfrançD 44: 446 1937) concl ded that this prurigo-like cutaneous response develops in certain patients when they cross the ocean, as a result of meterologic and climatic variations—and entomologic.

Chigoe—*Tunga penetrans* is the important species of burrowing fleas (Sarcopsyllidae) with short thorax. The abdomen of the gravid female bulges considerably The fecund female fixes herself in the skin, forcing herself into it little by little. After sucking blood for several days, she reaches the size of the fruit of a mistletoe and her body encloses multitudes of eggs. These hatch in 8 days and become adult in 3 weeks of further development. The chigoe almost completely parasitic, is indigenous to tropical America, and is occasionally encountered in the temperate zones. The primary cutaneous lesion is a shallow burrow of which the opening is blocked by the last 2 segments of the body of the parasite which swells with blood. It usually attacks the feet, particularly the toes beneath the free margin of the nail. Secondary infection extensive ulceration and even gangrene may supervene. The animal may be touched with turpentine and so induced to retreat (Stixrud) or it may be removed from the skin with the aid of a blunt needle. This should be done promptly before it burrows deeply and swells. Larvae may be found in the skin scraped from the vicinity of the burrow (Faust and Maxwell ADS 22 94 1930) Rupture of the creature while it is in the skin, or during the effort to remove it is to be avoided with care Wearing good shoes prevents infestation as a rule.

BLISTER BEETLES

Coleoptera.—In this order no member is a true parasite None inflicts a poisonous bite or sting but several species have an epidermonecrotizing principle in their chemical composition, so that they provoke blistering

Blister Beetles are of the family Meloidae. The thorax is narrower than the head or elytra, and the body is soft, slender, loose-jointed and sprawly i appearance. Many species exist. The adult feed on flowers and foliage Cantharidin is the volatile, crystalline substance to which the beetle owes its vesiculating property It ra ges from 0.4 to some 2.5% of the dry weight of the beetle and is sol ble in ether chloroform, be zene ad olive oil, but only slightly soluble in alcohol.

Cantharis (Meloe) vesicatoria is the so called Spanish fly abunda t in southern E rope and parts of Russia, where collectors, their faces and hands protected, shak the insect in the morning from the poplars ashes and lilacs where they feed in the early summertim onto sheets, whence they are collected, killed and dried. *Epicauta*, a potato beetle (not the Colorado potato beetle) is of this group. *Pomphopoea sayi*, sometimes a pest on peach trees in this country may cause serious poisoning of man. Among the rove beetles members of the genus *Paederus* contain a blistering principle not cantharidin.

The lif cycle of the Meloidae is not completely known; the insects appear and disappear suddenly and are present in numbers with seasonal periodicity Seasonal bullous dermatitis is a title und r which this beetle disease has been described.

The lesion which results from crushing a blister beetle on the skin is a large tense bleb which itches and burns. While lesions occur on exposed skin, they also occur beneath the clothing where the insect may be blown by a gust of wind. Microscopically one finds in the lesion intracellular and intercellular edema of the epithelial cells, extreme in degree. Absorption

through the skin may result in irritation of the kidneys. Stupid poisoning of 2 young women was reported by Nickolls and Teare (BMJ 2 1384 1954) who estimated that 0.5 mg of crystalline cantharidin might produce fatal blistering of the esophagus.

Benzene followed by soap and water will remove most of the vesicant, if used promptly. After the blister has developed it may be cut into from the side and 1% gentian violet in water may then be introduced into the cavity to prevent infection while the epidermis renews itself (Swartz and Wanamaker J 131 594 1946 Huse abs ADS 42 349 1940)

Tribolium destructor infesting a residence caused an urticarial eruption in an old lady whose skin reacted positively to a patch test of crushed beetle antigen (Bonar DWchr 1?? 837 103?)

See Castellani and Chalmers (Manual of Tropical Medicine, Wood, 1919 pp 326 2794) Baccaredda (Giornale ... 6 1422, 19 ?) *Paederus fuscipes* causing summer epidemics; Riley and Johannsen (Medical Entomology McGraw Hill, 1938 p 168); Huse (abs ADS 42 349 1940), *Paederus* ... causing dermatitis in July in Japan QMN (J 128 1131, 1948); Craig and Faust (Clinical Parasitology Lea & Febiger, 1951 p 826) Lehmann et al (AD 71 34, 1955) review and biology of *Epicauta* ... the commonest cause in southwestern U. S. A.



Fig 332.—Blister beetle bulla (Swartz and Wanamaker J 131: 594 1946.)

CATERPILLAR DERMATITIS

Lepidoptera the order which contains the moths and butterflies. They are characterized by the presence of scales on the body and wings and by the fact that the mouth parts are usually in the form of a coiled sucking tube. Metamorphosis is complete the larval stages being typically wormlike or hairy as caterpillars.

Nettling hairs of the larvae of some lepidopterid provoke dermatitis, perhaps in part by functioning as foreign bodies, probably as allergens, and certainly by virtue of poisons in them. Their properties of irritating may be destroyed by heat or alkali without altering their structure (Tyzzer JMedRes 11: 43 1907) No caterpillar bites or stings, despite the wicked appearance of some of them; but some innocent looking or even attractive have hairs which are highly irritating while others have spines that present at their tips spinules connected with underlying poison glands, the content of which may occasion caterpillar rashes.

Hylesian moths irritated the crew of a ship, reported Hill et al (J 138: 737 1948)

Caterpillar dermatitis occurring in Massachusetts and other parts of New England usually results from the nettling hairs of the caterpillars of the Brown tail moth *Euproctis crysorrhoea* and of *Megalopyge opercularis* many other species are also homininoxious. The first manifestation is pruritus, which develops 20 to 30 minutes after contact. Erythematous macules soon appear

usually followed by wheals. Cutaneous lesions are limited to the area of inoculation. Hairs lodged in the clothing may provoke generalized dermatitis. The disorder usually develops during the months of May and June at a time when the caterpillars are maturing. Numbness, nausea and vomiting may accompany severe percutaneous intoxication. Conjunctivae may



Fig. [illegible].—The brown-tail moth. (Dr Herman Pinkus.)

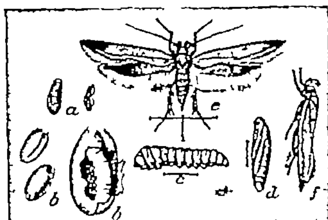


Fig. [illegible].—Brown-tail moth. (Webster.)

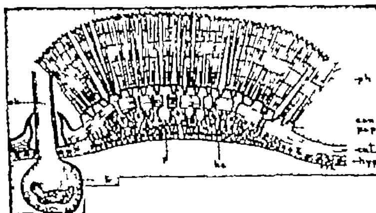


Fig. [illegible].—Brown-tail moth caterpillar section showing epithelium underlying nettling hairs. (Miss Kephart's drawing, courtesy of Drs. Riley and Johannsen, Medical Entomology McGraw-Hill Book Co Inc.)

be affected as the skin is. Blond, thin, sun-sensitive skin and also heat and humidity favor the development of dermatitis susceptibility to which is variable while some subjects undergo hardening (Touraine et al. Presse Méd 55 654 1947).

Contaminated clothing should be destroyed. The hairs are generally imbedded so deeply in the skin that considerable time must necessarily elapse

before the irritant is disposed of The application of 1:2,000 mercuric chloride lotion followed by painting each spot with flexible collodion, is a useful measure.

Moths and butterflies are of the same immunologic group for skin testing purposes (Parlato J Allergy 3 459 1932)

Lepidopterid larvae with poisonous spines that incite urtication include those of *Lagoa crispila L. pyxidifera Sibine stimulea Automerino* the larva of the Io moth, several Eucleidae and numerous members of the genera *Hemileuca* and *Hemerocampa* and of the families Liparidae and Arctiidae (Riley and Johannsen 1938)

Megalopyge opercularis the puss caterpillar is well known in the Rio Grande Valley Children call them asps and are respectful of their sting The envenomed patient suffers with aching pain of the affected extremity sweating nausea and distress comparable with that of a black widow spider bite McKinsey told me that a gram of calcium gluconate intravenously given prompt relief The caterpillars defoliate shade trees being fond of hackberry elm and plum and it requires spraying with 7 pounds of lead arsenate to 150 gallons of water a heavy dose to kill them (Hungerford) They are the most potent of North American caterpillars.

See White (BostonM&SJ 144: 599, 1901) Towle (BostonM&SJ 153 74, 1905) Potter (J 53 1463, 1909), Brewer (ChinMJ 37 351, 1923) Foot (JExperM 35: 737 19) Lucas (J 119 877 19) "puss caterpillar" Matheson (Medical Entomology Thomas, 1932, p. 419) D'Iseland (NOrlM&SJ 93 234, 1940) list of offenders; Steele and Sawyer (MaineMAJ 35: 157 1944) "Brown-tail moth" and hyposensitization therapy Fischer and McSweeny (MJAustral 2 13 1944) *Ochrogaster contraria* troubling military personnel on Broome Delbos (annderD 9 33, 1949) *Cnethocampa pityocampa* Micks (Texas J 1951: 1018, 1952) *Megalopyge opercularis* in Texas.

MYIASIS

Diptera (Flies) are insects with 1 pair of membranous wings attached to the second thoracic segment the second pair of wings being replaced by minute, club-shaped halteres mouth parts adapted for sucking metamorphosis typically complete Either they are acephalic as larvae or maggots, such as one finds on decomposing substances, or they are provided with a head with buccal pieces, eyes and antennae as are the larvae of mosquitoes and gadflies.

Two suborders are recognized ORTHORRHAPHA and CYCLORRHAPHA. The former includes species whose pupae escape from the last larval skin through a T-shaped opening Cyclorrhapha on the other hand escape from the pupal case through a round opening made by pushing off its anterior end. BRACHYCERA are those with short antennae composed of 3 segments. NEMATOCERA are those with filiform antennae composed of more than 3 segments.

There are many kinds of flies including *Musca domestica* the common housefly. Some of them bite painfully others transmit disease either as vectors or as mechanical conveyors, and the larvae of yet others can burrow in the skin.

Taxonomy is complicated; the following merely lists some families

CULICIDAE	mosquitoes
PSYCHODIDAE	sand flies, including the genus *Phlebotomus*, members of which transmit pappataci fever Carrion's disease and, perhaps, leishmaniasis
CHIRONOMIDAE	biting midges, gnats and punkies
SIMULIIDAE	black flies
TABANIDAE	horseflies and gadflies
MUSCIDAE	including biting stable flies
GLOSSINIDAE	tsetse flies
SARCOPHAGIDAE	flesh flies
OESTRIDAE	warble flies
OSCINIDAE	eye gnats which mechanically convey infectious agents of lacrymal secretions, sweat and exudates

BRACHYCERA Families of Parasitologic Interest after Brumpt

TABANIDAE	Squamae well developed		third longitudinal wing vein forked	ORTHORRHAPHA
ASILIDAE	Vertex almost convex	rudimentary squamae	anal wing cell ends in a point on the posterior edge	
LEPTIDAE	Vertex elevated			

SYRPHIDAE	Wings with a vena spuria and transverse veins	rudimentary frontal ampulla; body lacks macrochaetae (bristles); frontal suture absent: ASCHIZA	CYCLORRHAPHA
PHORIDAE	Wings lack vena spuria and lack transverse veins		
PUPIPARA	Abdomen nonsegmented Wings present or absent Head adherent to thorax	frontal ampulla well developed; body has macrochaetae; frontal suture present: SCHIZOPHORA	
MUSCOIDEA	Abdomen segmented Proboscis well developed Alar lobule generally rudimentary		
OESTROIDEA	Abdomen segmented Highly developed alar lobule		

TABANIDAE, including horseflies, gadflies and deer flies, are common pests of cattle horses and other animals, and often of man. They are big sturdy flies with broad abdomen, large hemispheric head, large eyes and short antennae. Only the females are blood suckers; males feed on flowers or plant juices. The family is of world wide distribution and contains some *,500 or more species. Their larvae are generally aquatic. Eggs are typically deposited in masses on water plants growing in marshy or moist ground. They are commonly laid in masses of several hundred, perhaps covered by a varnish or secretion, often light in color at first, becoming dark. In a week or so, cylindric larvae tapering at the ends, escape into water or damp earth and lead an active carnivorous life feeding on worms, snails and insect larvae until mature. The larval form may last for months; the pupal period is 1 to 3 weeks.

Many Tabanidae, particularly the Pangoninae inflict painful bites on man, actually drawing blood. Animals may be severely damaged by them. Secondary infection of the bites may occur. Tabanids are able mechanically to transmit tularemia, trypanosomes and other pathogenic agents, including *B anthracis*. *Chrysops dimidiata* and *C silacea* are known to inoculate *Loa loa*. Hypersensitivity to deer fly bites was cured by desensitization with an antigen of macerated and Seitz filtered flies by Mease (J 1[?]: 237 1943)

ASILIDAE, the hawk flies include a few insects known to be homininoxious.

LEPTIDAE, the snipe flies are of moderate size with conic bodies. *Symphoromyia pachyceras*, a California species, and *Atherix longipes* from the region of Oaxaca, Mexico, inflict painful bites.

SYRPHIDAE are dermatologically of no importance. The larvae of some of them devour plant lice.

PHORIDAE are of little dermatologic interest. *Aplochaeta scalaris* has produced cutaneous myiasis of animals and man in India. Asthma, associated with a positive skin test and proving capable of hyposensitization by immunologic methods, was reported due to the mushroom fly *Aphiochaeta agarici*, by Kern (J Allergy 9: 604, 1938)

PUPIPARA is the suborder comprising animals having leathery skins and laying completely formed pupae. Of its 4 families, the Hippoboscidae are the parasitic forms. They are all bloodsuckers, and the bites of those which attack man are almost imperceptible. Their importance as vectors of human diseases is doubtful, probably not great. *Hippobosca equina* is a species found in numbers about the tail ends of horses and cattle; wanting domestic animals to feed upon they utilize man. *H camelina*, common in Africa, inflicts painless bites which become slightly pruriginous papules.

MUSCOIDEA contains the houseflies and their allies. This large suborder includes many biting flies, among which the paraglossae are chitinous and sometimes bristly with tiny teeth that serve to perforate the skin, in contrast with tabanid and nematoceran bites in which the soft lower lips serve only as a sheath for the perforating buccal pieces.

The larvae of Muscoidea are of especial interest. The insects live generally in dependence upon vegetable or animal juices. Many lay their eggs or larvae on cadavers or animal substances where they hasten the putrefactive processes. Adult larvae dry up and are transformed into pupae, within which evolve the nymphs which mature into the imagines, perfect adult forms.

Muscoidea are divided somewhat artificially into 2 groups: Acalyptera, lacking winglets; and Calyptera, which have winglets. Among the acalypterous Muscoidea, there is little of dermatologic interest.

Sarcophagidae are calyptrates with smooth eyes; plumate antennal bristle either downy at the base or entirely smooth; abdomen uniform in color rarely has metallic luster usually is gray silky and of quite regular pattern. Of especial medical interest, sarcophagid flies include the genera *Sarcophaga*, *Sarcophila* and *Wohlfahrtia*:

Sarcophaga lambiens in cutaneous myiasis in Brazil.
S ruficornis in cutaneous myiasis in India.
S. t[?]bereae in cutaneous myiasis in Morocco.

Sarcophila meigeni l r in cutaneous ulcers in Europe
S rurails, infestation f wounds in E rope
Wohlfahrtia magnifica wound yiasl in Guinea.
W sha a and myiasl l Sudan has been used for rgical myiasis.
W v gil f runcul myia is. Larv burrow int the skin especially t the folds, provoking l flammation nd f runcular l ions they ca be removed from these by forceps (Hill rlborne and Brown: AJDisChild 91 339 1934)

Muscidae are calypterid flies with antennae in the form of a style plumed to its tip, the abdomen is short and lacks large bristles, macrochaetae at the margins of its segments. Many species para itize man in both their adult and larv l states.

In those which lay eggs the eggs hat h out primary larvae which enlarge rapidly under favorable circumstances, undergo a first moult, and become secondary larvae. They feed moult and become third larvae, the final stage When fully developed they empty their intestine take the form of a bulging sack and are then called pupae. From the pupa comes the nymph which develops into the imago, 4 moults having been required in the entire process.

The larvae are hard to classify in detail; in general, they are conic in front, cylindric in the midportion, thicker behin l. They have both anterior and posterior stigmata in the second and third larval states. The antennae are of 2 segments, small and conic Two boreal hooks are visible.

Muscidae may be divided into those which bite and those which do not.

Bit ng Fl s.—Interesting biting muscidae include *Glossina* tsetse flies, with the species *fusca palpal s* a l *morsitans* being exceedingly important as vectors f the trypanosomes whi h cause leeping sickness; and *St morys* including species which carry eggs and larvae of *Dermatobia*

Nonbiting Fl es.—These include the following:

Auchmeromyia l teola of Afric li in bout the h bitations of man. Its larvae li e in the soil and are blood suckers at night They probably lo not act as vectors.
Call phora eryth oceph la causes myia l of wounds. Larvae ha e been used in treating osteomy el ti Other species of *Call ph ra* also cause myiasis.
Chrysomyia bez ia a larv may in est wou ds of animals nd man the larvae may cause furuncular myiasis and may l ale nasal sinuses ven eroding the nasal bones.
Cochliomyia hom nivorax often infests wounds in America. The larv e, called screw worms, are whit and are formed of 12 segments of which the upper edges bea circles of ery small pi es The rrangement of these gi es some justification for the ulga name Infesting hogs in particula they lso ttack man The screw worm is the larv of *C americana*, not of *C macellaria*, according t Cushing nd Patton (AnnTropM 7 339 1933)
C rdylobia anthropophaga adults li on decaying substances. Their larvae invade the skin of man and various animals l Africa Cayor worms, as they are called, hatch from eggs l id on the ground They acti ely force thei way int the kin, where they develop for fortnight or so, then crawl out through a f runcular lesion which they provok transforming themsel es into pupa withi 24 hours nd hatching withi 3 weeks. The N tal larv is simula
Lucilia are call phorine muscids of medium size and lustrous metallic green color the green bottle flies *L caesar* nd *L sericata* often found in wounds. The latter recog ized beneficial by Larry (1842) was purposefully utilized by Baer (JB&JSurg 13 438, 1931) in the treatment of wou ls.
Musca is the genus of the domestic fly d ngerous because of its mechanical transference of pathogenic organisms, such as *B typh sus* ont food in its feet or dejecta. A useful control gent i tangl foot, a mixture of 5 parts of resin in 1 of castor oil. The filthiness of flies l undeniable, and they ought t be combatted energetically *M d mestica* caused nasal llergy and positi skin tests (Jameson JAllergy 9 272, 1938)
Phormia regina produces severe cutaneous myiasis of sheep in Texas. It has been found in man, particul rly in the intestine

OESTROIDEA co tains the Oestrinae (botflies, heel flies) which are of especial signifi cance in connection with creeping eruption and other forms of myiasis of man and animals.

Adult hav a l rge hemispheric head with a pair of faceted eyes separated by a brow bearing 3 ocelli. Antennae are sh rt third segment bears bare or plumed style Proboscis sometimes well developed somet mes hidden in a buccal fossa (CUTEREBRINAE) but generally small en rud ment ry (OESTRINAE) Wi g veis almost a in Muscidae; winglet al wa s present. Imago lives only a short time apparently does not feed. Viviparous females la ggs on mammals.

Larvae obligatory par sites develop in the kin, nasal sinuses or intestine Larvae hard t d sti gu sh fo classifi ti Thei bodies have 12 ann lar segments the first ge erally l ttle separated or act ally combined. More or less cylindric. N rrower i front tha in th rear are *Hypoderma* and *Gastrophilus* enlarged in front are *Dermatobia* and *Cephenomyia* The body is formed of well-separated annular segments, generally with lateral pad and warty formations. Ante nae short, of wart shape and have 1 or chitinous rings suggesting ocelli Posterio stigmata are important fo classification. In *Gastrophilus* they are placed in a cavity in the rear ring and have 3 curved, concentric slits. In *Dermatobia* they are enclosed in a cavity formed by the next to the last ring and re m ked sl ghtly differe tly

Oestrinae clude dermatologically interesting species as follow :

Gastrophilus haem rrhoidalis causes creeping eruption in Europe nd North America.
G intestinalis the larv of which li e in the stomach of the horse, may cause creeping eruption, especially in hostlers.
Rhinoestrus purpu es has caused oculomyiasis
Hypoderma bo is common throughout Europe and in parts of Africa, lays eggs especially on the hairs of cattle, without biting them The larv e produce tumors with small orifices, especially on young animals These larv frequently occasion creeping eruption in man
H lineata is common in North America, causing great economic loss by damaging hides t has been found in man in Europe
Oestrus ovis the sheep bot, or gad fly causes ophthalmomyiasis.

CUTEREBRINAE.—The interesting species is *Dermatobia hominis* a botfly which causes furuncular myiasis. The female lays eggs on insects, where they hatch; and the larvae leave their insect host for a warm blooded one where individually they pierce the hide and finish their evolution within the skin near the site of entry They frequently attack the ox, dog and man. The eggs are conveyed commonly by species of the mosquito, *Psorophora;* but other mosquitoes, bloodsucking muscoids several non-bloodsucking muscoids and the tick, *Amblyomma cajennense* may also serve In the skin the larva feeds, grows, and moults twice The mature third stage larva is from 18 to 24 mm. long and is flask shaped possessing well-developed oral hooks and dark brown anterior cuticle. The dark brown anterior spiracles each consist of rows of 6 small, dark brown processes located on the mesothorax. Near the anterior border of the second and third thoracic segments, and more conspicuously on the first 4 to 6 abdominal segments, are short, stout posteriorly-directed spines, or booklets which anchor the larva in the skin (Craig and Faust) Larval development requires about 50 to 75 days after which the larva works its way out of the skin falls on the ground and pupates in the soil.

Myiasis.—Larvae of brachyceran flies are able to parasitize man in various ways their parasitism is either necessitous or facultative Those of obligate parasitism provoke myiasis cutanea and some forms of myiasis of natural cavities larvae of facultative parasitism produce myiasis of sinuses, natural cavities and intestines.

CREEPING ERUPTIONS.—Three varieties of migratory animal infestations involve the skin: (1) those due to nematode parasitism (q v) (2) those due to acarine burrowers scabies and Tetranychus (q v) and (3) those due to larval flies, mainly oestrids of the genera *Hypoderma Gastrophilus* and *Dermatobia* Avoiding the ambiguity of creeping eruption, I prefer the names cutaneous helminthiasis for the nematode diseases, and cutaneous myiasis for dipteran infestations. See pp 581 583 584 617

CUTANEOUS MYIASIS is characterized by the development of dipterous larvae within the skin or subcutaneous tissues. The clinical aspects are varied

Cutaneous myiasis has received many names, some of which suggest particular parasitologic forms. Synonyms include dermamyiasis linearis migrans oestrosa and hypodermyiasis or ox-warble disease. Larbish or oerbiss, is a form of creeping eruption occurring in Senegal, probably due to the presence of dipterous larvae under the skin. Larva migrans is used usually in reference to creeping ancylostomiasis due to the dog hookworm (See p. 581)

CREEPING MYIASIS, first described by Lee (TransClinSocLond 8 44, 1874 18 74 1884) is a type of myiasis beginning with a small, painful, subcutaneous lesion which moves in a continuous fashion its course being marked by a red and ecchymotic line which disappears in a few days. The migration of the pain and of the red line is pathognomonic, the line is narrow somewhat elevated, tortuous, whitish or pinkish and threadlike and it marks the migrations of an immature larva within or just beneath the horny layer The tunnel made by the parasite is from 0 2 to 0 3 cm. in diameter and varies in length with the distance traveled by the animal. Ordinarily the larva moves at the rate of from 1 to 10 cm per day When the larva is ready to depart the tender spot remains stationary A little tumor develops there the summit perforates, and seropurulent liquid is discharged along with the larva itself.

The larvae of *Hypoderma bovis* (De Geer 1776) *H lineata* (de Villiers, and *H diana* (deer warble, Brauer 1858) are known to attack man. The larvae usually gain access by burrowing directly through the skin, to which, after diverse peregrinations, they return and give rise to subdermal and dermal lesions that lead to their discovery

The disease is common in the Shetland Isles and Norway and is caused in these regions by larvae of *Hypoderma bovis*. The same species has been found by Fülleborn in Africa and Brazil and it also occurs in France. A case due to *Gastrophilus intestinalis* was seen in Canada. In Russia and Siberia where this myiasis apparently is of frequent occurrence it is generally due to larvae of *Gastrophilus*. The empty eggs of *Gastrophilus haemorrhoidalis* have been found on the surface and hairs of the body

Young and Sudler (J 49: 1914, 1907) reported intranasal infection from the screw worm fly *Cochliomyia americana*. Singleton (J 61: 1782, 1913) reported a penile lesion due to *Dermatobia noxialis* the macaw worm, in a German laborer. Dyer (NOrMedJ 71: 105, 1918) described a case of fly-blown ulcers of an old man's leg from which King of the Bureau of Entomology identified the flies as *Lucilia caesar*, *L. pilatei* and *L. sericata*. In a case seen by Magath (AJS 2: 16 1930) *Dermatobia hominis* was the offender. Stewart (J 93: 709 1929) reported an extensive case due to *Phormia regina* (Meig) in which the scalp and ears were involved.

Gastrophilus larvae can be seen in their intraepidermal tunnels by applying a drop of oil to the skin through which the black transverse bands of spines on their segments are visible (Austmann J 87 1106 1926). They may then be removed by using a sharp needle. Injections of chloroform have been used with success.

SUBCUTANEOUS MYIASIS is characterized by ambulatory tumors the larvae eventually producing furuncular lesions from which they are discharged. Until that time they wander beneath the skin and give rise to fugacious, reddish, sometimes edematous tumors. The formation of these lesions is preceded locally by itching and shooting pains sometimes of considerable severity even causing the victim to cry out. Within several days the lesions disappear only to reappear at a more or less distant location. After persisting for 10 to 20 weeks, there occurs at the summit of the final tumor a reddish punctum which opens and permits one to see a pseudocore which is the whitish posterior extremity of the living larva. Cases of this sort are frequently seen by doctors and are also known to the rural people of Norway, Ireland, Brittany and Scotland. The larvae generally are of the species *Hypoderma bovis* or *Hypoderma lineatum*.

FURUNCULAR MYIASIS.—Brumpt limited this name to cases in which the cutaneous tumor is the primary and only manifestation occasioned by the larval parasites. This can be produced by larvae which have evolved at that location such as those of *Dermatobia* or by a larva which has migrated through the body without giving rise to other phenomena. In Europe this form of myiasis is generally caused by *Hypoderma diana* rarely by *Hypoderma bovis*. In America it is caused by *Hypoderma bovis* and exceptionally by larvae of *Dermatobia*. The latter do not migrate subcutaneously but they push into a hair follicle and form a purulent sac resembling a furuncle within which they evolve.

When the larva becomes adult it falls away spontaneously. The spot undergoes cicatrization, unless it is secondarily invaded by larvae of *Cochliomyia americanus* which may be numerous in the same region. The lesions are both sore and intensely pruritic. *Wohlfahrtia vigil* causes almost all cases of human myiasis affecting infants less than a year old, according to Vander sluis and Whittemore (MinnM 21 415 1938). The lesions were on the chest in their patient as is usually the case.

Cordylobia (cayor worms) may lodge in various parts of the body particularly the lower extremities. Without migrating the larva provokes a furuncular tumor of short duration which undergoes rapid evolution.

Gastrophilus larvae probably issue from eggs laid on the human skin or happening to be there, and they penetrate to the level of the depth of a hair follicle and continue their subcutaneous course provoking the red line characteristic of creeping eruption.

Hypoderma lineatum and *H. bovis* infestations result from ingestion of eggs or of young larvae which require some 6 months to reach the skin. Their presence is then revealed by the appearance of the tumor which has a minute opening through which the larva escapes. It is probable that man is capable of being infected by way of the digestive tract the hands, soiled with larvae or eggs by contact with animals conveying them to the mouth.

MYIASIS OF WOUNDS AND ULCERS.—The eggs of *Lucilia sericata*, *L. regina*, and *L. caesar* deposited in a wound will hatch in a few hours, and the larvae

will penetrate into the lesion and thrive there This may of course occur naturally as well as experimentally, either from accidental introduction of eggs or larvae into the wound or through the actual deposition of eggs or larvae by the flies. Purulent lesions, such as syphilitic sores and other stinking ulcers, attract them This form of myiasis is by far the most common in man and the animals, particularly in the tropics and among people who are careless with their injuries. In temperate regions, the fly is usually *Wohlfahrtia Sarcophaga* or *Calliphora* in hot regions, one finds *Cochliomyia Chrysomyia Sarcophaga Lucilia* and *Pycnosoma*



Fig. 357 —Furuncular myiasis due t *Dermatobia cyaniventris*. (Costa ADS 50 36, 1944.)

Surgical Myiasis.—As a therapeutic measure, larvae of certain flies have been put into ulcers, for they possess the ability to eat decadent and purulent parts of the wounds without attacking healthy tissues. Maggot therapy introduced by Baer (JB&JSurg 13 438 1931) has been used in America in many cases of osteomyelitis and other chronic affections. Technique must be meticulous, the flies being raised most carefully to avoid their infection with aerobic and anaerobic germs. Suitable larvae are placed in the wounds, and, when they have cleaned them satisfactorily they may be removed. Time expense and pain are disadvantages, while rapidity of débridement discovery of hidden sequestra and pockets of pus, stimulation of granulations, continuity of treatment and diminution of hospitalization and morbidity are the advantages, Maddock and Jensen (ASurg 37: 811 1938) decided after studying 99 cases of osteomyelitis treated with maggots.



Figs. 858-860.—*Dermatobia hominis*: furuncular lesion, excision of larva, and close-up of the larva. (Harrell and Moseley, South. M. J. 35, 1942.)



Fig. 861.—*Chrysomyia macellaria*, larva, pupal case, and adult. (Dr. F. W. Shaw.)

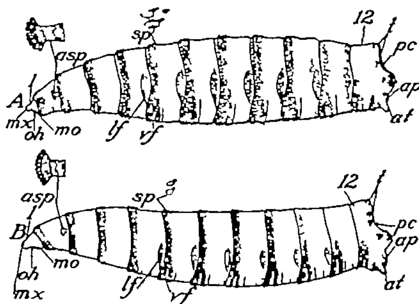


Fig. 862.—Lateral view of mature third instar larvae of (A) *Cochliomyia americana* and (B) *C. macellaria*. ×6. Abbreviations: ap, anal protuberance; asp, anterior spiracle; at, anal tubercle; lf, lateral fusiform area; mo, mouth; mx, maxillary lobe; oh, oral hook; pc, posterior cavity; sp, spiracles; t, tubercles; vf, ventral fusiform area; 1, first (or cephalic) segment; 12, twelfth segment. (Drs. F. W. Laake, H. C. Cushing and H. L. Parish, U. S. Dept. Agriculture Technical Bulletin 500, January 1936.)

Extracts of cultured larvae have been studied and seem to yield good results. It is believed that the active principle of the allantoin derived from the larvae is actually urea, and this clear crystalline substance may be used as the solute of wet applications. It is my opinion that any other bland isotonic nontoxic soluble crystal could be substituted with equal success when used for moist poultices.

MYIASIS OF SINUSES AND OTHER LOCATIONS.—Nasal myiasis is common. The oestrid affecting sheep is a viviparous insect which lays its larvae in the nasal fossae. When the young shepherds of Kabul are inattentive, the Oestridae lay eggs on their eyes, lips and even in their noses; and these provoke edema of the mouth and lips, erythema, conjunctivitis, and pain in the nasal fossae. The disease has been observed not only on the plateaus of Afghanistan but also in the central part of the Sahara where the flies abound from March to June and vastly discommode natives who inhabit regions at an elevation of 5,000 to 8,500 feet. Oestriasis as of sheep is frequent in man also in the Cape Verde archipelago, where it is seen in the nose pharynx and about the eyes.

Myiasis of wounds as well as of natural cavities may be caused by larvae of Diptera having facultative parasitism. The symptoms and severity vary with the localization or widespread distribution of the larvae.

Eggs of various flies may be laid in the nasal fossa. When the larvae develop, the patient first experiences severe discomfort and headache then pain which is practically intolerable. The bites of the larvae on the mucous membrane provoke sneezing and nosebleed. Inflammation affects the external parts of the nose within a few hours, and it swells. Larvae emigrate into the posterior nasopharyngeal cavity and the patient complains of pain in the throat. After devouring the mucous membrane of the nasal cavity the larvae continue their destructive work, invading the frontal sinus, and even necrotizing the palate, which may be perforated. Severe reflex difficulties ensue, with convulsions, vertigo, visual troubles, meningitic symptoms, sometimes aphonia and deafness. To appreciate the havoc, one needs only to see the volume and number of the larvae expelled, their mass representing a pint or quart of eaten substance. The disease has been observed in all countries. It is particularly common in the tropics

The auditory canal and middle ear may be involved. Otomyiasis in man is characterized by intolerable pain and the swelling of the ear suggests acute otitis. Larvae may perforate the tympanum or enter the mastoid cells, even getting into the venous sinuses and the meninges. Atrocious suffering is followed by death.

The eyes may be affected, but rarely as an isolated phenomenon. Larvae may enter the orbit by way of the sphenoid foramen and actually devour the bulb. Various larvae can cause acute and extremely painful conjunctivitis. Some Oestridae which ordinarily lay their eggs in the eyes of animals may deposit them in those of human beings.

The urinary passages and bladder may be involved, as the skin is, by wandering larvae which are eventually passed with the urine.

The affection produced by ingestion of larvae or by their development in the intestinal canal results generally from eating soiled food. Larvae in the stomach are likely to provoke nausea, dizziness, epigastric pain vomiting and diarrhea which rids one of the parasites; the cheese fly *Piophila casei*, is such a fly. When they reach the intestine they may produce symptoms as of severe helminthiasis, severe abdominal pain hemorrhage or typhoidlike accidents. When they remain for a long time which is rare, the symptoms simulate mucomembranous colitis (Bryant J 109: 578, 1937)

Treatment.—In myiasis of wounds, one flushes away the maggots and picks them out with forceps as well as may be. Stewart and Boyd (J 103 402 1934) found 15% chloroform in vegetable oil an efficient douche. Injections of chloroform and benzine are efficacious. *One may inject infusions of* basil or a weak phenol solution. In nasal myiasis, chloroform inhalations kill the larvae and enable them to be washed away with water (Dixon J 83 1332, 1924). Inhalation of the fresh plant *Ocimum basilicum* will promote the evacuation of larvae in nasal myiasis according to Mackie et al., quoted by Andrews (Diseases of the Skin, Saunders, 1954)

See Blacklock and Thompson (AnnTropM 17 443 501, 1923) Tumbu fly *Cordylobia anthropophaga*, infestation of experimental animals, producing vigorous inflammatory reaction and immunity to subsequent attack Blacklock and Gordon (Lancet 1 923, 1927) furuncular myiasis from Tumbu fly Cushing and Patton (An TropM 27 539 1933), *Cochliomyia americana* and other flies producing myiasis; Puent ... Revargentdermatosif 18: 44, 1934) *Dermatobia hominis* Aubertin and Buxton (AnnTropM 28 245, 1934), taxonomy of Cochliomyia; Platt and Scott (BMJ 2 1098, 1935) *Lucilia sericata*, green bottle fly causing otitis; Laake et al (U.S. Dept Agric Tech Bull 500, 1936) *Cochliomyia americana* and *C macellaria* Walker (JParasitol 23 163 1937) W tiell Weber (BJL 51 132, 1939) migratory subcutaneous nodules, cause undetermined Chow (ChinMJ 57: 145, 1940), flies as mechanical carriers of pathogenic bacteria; Downing (ADS 43 180, 1941) *D hominis* case, furuncula Harrel and Moseley (SouthMJ 35 720, 1942) *D hominis*, Smith and Rosenberger (AmJTropM 22 463, 1942) *Cordylobia anthropophaga* case, furuncular; Turnbull and Franklin (J 120: 117 1942) *C americana* otitis; Costa (ADS 50 36, 1944), *Dermatobia cyaniventris* case, furuncula Young (ADS 49 369 1944), cutaneous lesions, identification of maggots; T ... (BMJ 2: 11, 1945) *H bovis* case, migratory nodules; Goldman (AmJDisChild 69: 290 1945)

D. hominis case; Smith and Greaves (BMJ 2: 20, 1946) *H. bovis* case; Lewis (ADS 54: 2[illegible], 1946). *M. [illegible]phagus* causes the sheep "ked," bites on legs of wool worker; Popov (AOtol 45: 112, 1947) nasal myiasis, 3 cases, 1 fatal; Taylor (AnnOtol 59: 531, 1950) *C. americana*, screw worm, in nasal cavity, Conway (BMJ 2: [illegible], 1950) *Oestrus ovis* larval conjunctivitis in British soldiers in Egypt. West (The House Fly, Its Natural History, Importance and Control, Comstock, 1951) comprehensive; Brumpt (Précis de Parasitologie, Masson, 1949 p. 1375 ff.)

GNATS AND MOSQUITOES

NEMATOCERA.—These, the second division of Diptera, are insects which have long antennae of 6 to 15 segments. The body is slender and the wings long and narrow. The larvae generally live in water but some develop on land or in decomposing vegetation. The wing pattern is important in determining genera and even species. The families of parasitologic interest were classified by Brumpt as follows:

BIBIONIDAE	tibiae lack spurs		no discoidal wing cell	have ocelli
BLEPHAROCERIDAE	anterior tibiae spurred			
SIMULIIDAE	tibiae and metatarses large and flat		costal wing vein ends near the tip of the wing	lack ocelli
CHIRONOMIDAE	tibiae and metatarses slender subcylindric			
CECIDOMYIDAE		fewer than 6 final divisions of wing veins	costal wing vein goes across the wing	
PSYCHODIDAE	wings oval or lanceolate, hairy	more than 6 final divisions of wing veins		
CULICIDAE	wings rounded at summit, scaly			

BLEPHAROCERIDAE are little gnats which dance in the air particularly about water-wells. A few species of *Curupira* are bloodsuckers.

SIMULIIDAE are gnats of humpback appearance and generally dark hue. Their eyes are holoptic, joined in the midline, in males only. Antennae, cylindric and relatively short, are composed of 11 segments. The wing pattern is peculiar to the family. The buccal pieces are complete and powerful in the females. The mandibles and jaws are lanceolate. The epipharynx has hooks at its point for perforating the skin. Long and flexible maxillary palpes are formed of 4 segments. Salivary glands secrete substances variably toxic with different species. Development of larvae occurs only in well-aerated water. Eggs are laid on submerged aquatic plants. Hatching is comparable with that of mosquitoes, the larvae fixing themselves to plants or stones in the current of water by means of their posterior sucker. For certain species, it is known that the larvae moult 6 times. Their need for water and herbage is their vulnerable aspect from the point of view of control, best obtained by clearing and cleaning the streams.

Simuliidae are known to transmit *Onchocerca volvulus* and *O. caecutiens*. The bites of some species, *S. amazonicum* for instance, are very painful, last for weeks, and are surrounded for several millimeters by ecchymosis; the bites of others may be manifest as droplets of blood upon itchy papules, which resorb more or less quickly according to the sensitivity of the individual. Only females bite man and animals. Bites of swarms may be seriously and even fatally toxic to creatures, including man, that are not immune to them. Oily emulsions of tar or creosote protect one; in some regions, cattle may have to be put to pasture at night at certain seasons, and their stables fumigated with smoke from fires.

The lesions resemble purpura, being petechial, or erysipelas, being confluent if numerous and associated with pain, edema, vesiculation, lymphadenitis, even chills. In the vicinity of Tokyo, simuliid fly bites induce immediate pruritus, blood-crusted nodules and giant urticarial lesions with ill ease; later there may occur eczematoid lesions, chronic noduloveiscular plaques, or hard, warty nodules (Gudgel and Grauer: ADS 70: 609, 1954).

Simulium damnosum (Theobald, 1903) transmits *Onchocerca volvulus* to man. It is a gnat 3 mm. long, blackish, the thorax covered with gold hairs, abdomen with black, anterior tarses dilated, posterior metatarses with yellow rings, dentate claws. Common throughout equatorial Africa.

S. amazonicum bites produce ecchymoses lasting for weeks.

S. avidum, *S. mooseri*, and *S. ochraceum* of Central America, are intermediary hosts of *Onchocerca caecutiens*.

S. neavei, in East Africa causes in man a dermatosis like craw-craw.

S. pecuarum in the United States is one of many species called buffalo gnats, which may poison horses fatally.

CHIRONOMIDAE are distinguished from mosquitoes by their short proboscis and the absence of scales, though in size and general appearance they are similar. Only the females are hematophagic. *Culicoides austeni* in Africa, is an intermediary host of *Acanthocheilonema perstans* a filaria producing elephantiasis. *Culicoides grahami* and many others of the family bite man. Some are accused of carrying leishmaniasis in South America.

PSYCHODIDAE have the general appearance of little night flying moths or mosquitoes, from which they differ in having oval or lanceolate wings and hairy body, without scales on their wings. The larvae live on decaying vegetation. Only the genera *Phlebotomus* and *Pericoma* contain homininoxious species. *Pericoma* is not particularly interesting. Phlebotomi transmit three-day fever, American leishmaniasis and oriental boil.



FIG. 641.—Sandfly bites on the leg of a hyperreactive Israeli girl. (Dr. S. Gill.)

Phlebotomi have palpes with 4 segments, longer than the proboscis. Antennae with 16 segments. Elongated proboscis. Wing pattern: first longitudinal vein simple, second twice-forked, third simple, fourth forked, fifth and sixth simple; transverse veins approach base of wing, basal cells therefore short. Wings are raised and form an angle of 45 degrees. Length 1.5 to 3.0 mm. They are cosmopolitan. They are generally nocturnal, hiding to avoid desiccation during the day. Only the females bite. Their flight jerky and of short range, is quite characteristic. It is silent.

The bite is painful, and in nonimmune persons there may result a papular eruption with excoriations which simulates scabies. Their biology is not fully known, and their control is not specific. Destroying the woods where they live and putting the soil into cultivation is successful. Particularly well known species are: *Phlebotomus argentipes* a vector of kala-azar; *P. papatasii* a vector of pappataci fever and leishmaniasis; and *P. perniciosus* a vector of infantile kala-azar.

MOSQUITOES AND MOSQUITO BITES

CULICIDAE, the mosquitoes, are scale-covered insects which carry malaria, filariasis, yellow fever, dengue and probably other diseases. The males have plumed antennae, those of the females are almost smooth. The wings are long and narrow. Among the medically important CULICINAE, the proboscis is longer than the head and thorax combined. The bite is painful, but there generally occurs quite rapid development of tolerance for the venom. Species of *Psorophora* mechanically transmit eggs of the bot fly *Dermatobia hominis*. *Aedes aegypti* is suspected of mechanically transmitting the spirochete of yaws. Tularemia may be so conveyed.

ANOPHELINE mosquitoes are characterized by having maxillary palpes as long as the proboscis in both sexes. The larva, lacking respiratory siphon, disposes itself horizontally against the undersurface of the water; the adult holds itself obliquely with respect to the surface on which it stands.

CULICINE and AEDINE mosquitoes are characterized by the existence of maxillary palpes longer or shorter than the proboscis in the male and much shorter than the proboscis in the female. The larva, having a long respiratory siphon, holds itself obliquely with respect to the undersurface of the water; the adult stands with its body more or less parallel with its support.

Mosquito Bites.—Species of mosquitoes too numerous to list inflict bites which become itchy wheals. Individuals differ in susceptibility and some apparently develop immunity. Schaudinn found the contents of the insects esophageal diverticula intensely active in causing pruritus. The lesions resulting from mosquito bites were classed by Hecht (DWchn 88: 793, 1929) as (1) wheals which vanish quickly; (2) wheals followed by more persistent swelling; and (3) bites that are followed a day later by red, itchy welts. He estimated that the quantity of saliva injected is about 1/6 of 0.0001 cu. mm., so that it must be considered a potent poison. Various separate tissues of mosquitoes provoked the same reactions as the sting (Benson: AIntM 64: 1306, 1939). Investigating the bullous reaction which is uncommon, Hecht (DWchn 96: 588, 1933) confirmed the observation of Bode (DWchn 96: 7, 1933) that vesicles following bites of *Culex pipiens* are transferable by means of the vesicle fluid. Benson (JAllergy 8: 48, 1936) reported success with immunization against the vesiculating effect but not against the primary wheal; he believed that specific sensitivity to the mosquito occurs. Brown et al (SouthMJ 31: 590, 1938) reported a case in which gangrenous lesions followed the bites of *Aedes aegypti* and they attributed this to the Arthus phenomenon. A flight of *Psorophora columbiae* reported by Bishopp (Sci 77: 115, 1933) fatally bled and intoxicated at least 173 head of livestock and poultry and severely sickened many of the men who made smudges to protect their cattle near Miami, Fla., during September, 1932.

The preference of mosquitoes for some individuals was discussed editorially (BMJ 1: 1131, 1951), the insects being attracted to numerous unwashed sleepers rather than to a few clean ones (Muirhead Thomas: BMJ 1: 1114, 1951). Reactivity requires about 11 days to develop, after which one may observe both immediate urticarial and delayed tuberculoid reactions (Heilesen: abs YBD 1950, p. 401). Reactivity to mosquito extracts appears to be due to multiple allergens, and is inhibited by ACTH but not much altered by antihistamine compounds (Rockwell and Johnson: JID 19: 137, 1952). The local injection of hydrocortisone profoundly inhibits reaction to mosquito bite (Goldman: J 149: 265, 1952).

Symptoms provoked by bites of mosquitoes and other insects are pretty well relieved by applying ammonia, 1% menthol in alcohol, hydrogen peroxide, glycerol or soft soap. Tincture of iodine is good. Thiamine in adequate doses is said to diminish itching, papule formation and susceptibility to bites (Shannon: MmnM 26: 799, 1943). Desensitization may be accomplished with the species-specific venom, which resembles that of bees (QMN: J 120: 726, 1942). Repellents such as citronella are not very successful, but a DDT pyrethrin aerosol spray is. Camphorated chloral (Brit. Pharm.) is the liquid resulting from trituration of equal parts of camphor and chloral hydrate, with or without dilution with some bland oil; it gives relief when applied locally. An old fashioned repellent may be prepared as follows (QMN: J 109: 290, 1937):

℞

Oil of citronella	15.0
Spirits of camphor	7.5
Cedar wood oil	7.5
Petrolatum	60.0

Secondary infection must be treated as such; see staphylococcic and streptococcic dermatoses.

Meticulous control of breeding places smudges and protection with netting are necessary to control mosquito-borne diseases. Control likewise of infected persons must be considered in order to prevent the insects from becoming infected (Herms and Gray Mosquito Control, Oxford U Press, 1940)

ANTS, BEES AND WASPS

Hymenoptera.—This is the order which includes all the truly stinging insects, such as bees, hornets, wasps and some of the ants. These insects have 2 pairs of membranous wings held together on each side by small hooklets on the anterior margin of the hind wing The mouth parts are adapted for chewing or for both chewing and sucking Metamorphosis is complete. Stings are inflicted only by the females.

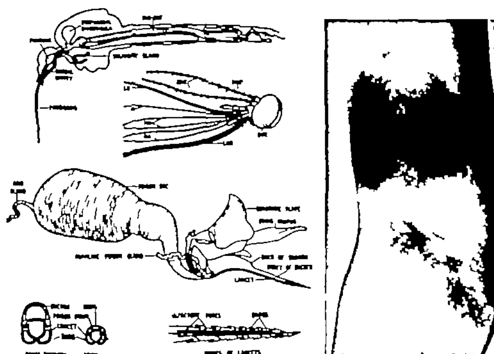


Fig 364 —*A* (above) shows the mouth parts of the mosquito. *B* (below) shows the stinging mechanism of the honeybee. (Benson AInt M 64 1306, 1939)

Fig. 365 —Reaction on the arm 24 hours after intradermal injection of the venom of a mosquito, *Aedes cereus*. (Dr R L. Benson.)

It is the abdomen of the female which is usually provided with a sting or saw which is in fact a modified ovipositor and is connected with glands which secrete poison. The sting of the worker honeybee lies within the sting chamber at the end of the abdomen a chamber produced by the infolding into the seventh abdominal segment, of the greatly reduced and modified eighth, ninth and tenth segments. From it the dart like sting quickly can be exserted. The sting itself is made up of a central shaft beside which are paired lancets, or darts, provided with sharp, recurved teeth and lateral to these lie the paired, whitish, fingerlike sting palpi. There are kinds of glands, those secreting poison and those secreting alkali matter and there is also a reservoir for poison. While it contains formic acid, this is not the poison principle, which is complex being composed of at least 3 substances: phlogogenic provocative of inflammation in man; stupefacient; and convulsant.

Stings.—Prolonged urticaria and even fatalities have been known to result from stings. Bees and wasps envenom as well as sensitize The swarming of bees upon the body and head may kill by suffocation Violent motor responses to stings, startling as they are painful have resulted in cardiovascular accidents (J 150: 1646 1952 151 878, 1953) and deaths (Milne BMJ 1 1123 1949) Deaths following wasp stings have also been recorded

by Alexander (BMJ 1 1346 1938) and Wegelin (abs J 140 574 1949) Ant stings proved fatal in a case reported by Bowen (SouthMJ 44 836 1951) whose discussion of allergy to arthropods and bibliography are interesting. At autopsy following bee stings, there have been found emphysema, possibly with frothy exudation, overdistention of the right side of the heart and visceral passive congestion (Tex Blake EAfrMJ 19 74 1942)

Histologic studies of the lesions produced by bee stings were made by Crewe and Gordon (JTropM 43 341 1949) who found in guinea pigs edema, cellular infiltration and even muscle necrosis. Walling off of the damaged tissue by a palisade of inflammation contrasted with the absence of such a barrier following the attacks of some blood-sucking insects.

Flury (MedKlin 31 972, 1935) stated that the toxin is like a saponin, and is not acetic acid but is related probably to stearin derivatives a considerable portion of the purified venom of bees is certainly lipoidal Set onto the skin, it is nonirritating when the epidermis is broken, however high dilutions produce typical effects as they do likewise when applied to normal mucous membranes.

That immunologic and allergic responses to insect proteins and venoms occur is indubitable. Hubert (LyonMéd 138 678 1926) reported a patient who was stung twice by wasps and after the second experience had general urticaria and anaphylactic shock similar cases are on record Passive transfer of sensitivity to bee venom may be accomplished (Benson and Semenov JAllergy 1 105 1930) but is imperfect for mosquitoes and desensitization can be achieved with regard to the late papular reaction but not to the immediate wheal (Benson AIntM 64 1306 1939) While the usual response to a sting is local swelling redness and pain systemic reactions may occur and generalized erythematous rashes have been observed (Taylor BMJ 2 368 1939 Sonck abs BJD 64 121 1952) See QMN (J 111: 1125 1938)

Of some 5 000 species of bees, most possess stinging and poison apparatus, along with a choleric point of view When a honeybee stings the tip of the abdomen and the entire sting apparatus are torn off and remain in the wound the muscles continue to act for a time forcing the sting deeper One should lift out or scrape out the sting rather than pinching it by grasping it, a procedure which would force more poison into the wound. Local applications other than hot packs or suitable antiseptics probably have little real effect.

Clad in black, one is far more likely to be stung than if dressed in white Black animals are discriminated against (Riley and Johannsen)

Bumblebees do not lose their sting but can apply it repeatedly

Stinging ants are common in the tropics, and those which lack stings have well-developed poison glands. Ants lacking stings are those of the subfamily Camponotinae which includes most North American species some of these have extremely large poison glands and reservoirs and in attack they spray poison from the tip of the abdomen into the wounds made with their strong mandibles. Following the bites of numerous ants, a man developed stertorous breathing frothy expectoration, cyanosis and shock which was relieved by the intravenous injection of 300 mg of procaine in 300 cc. of 5% dextrose (Morhouse J 141 193 1949)

Velvet ants, so-called hairy and usually brightly colored Hymenoptera of the family Mutillidae are notorious for stinging *Sphaerophthalma occidentalis* a black species with a scarlet band is common on the beach sands of Lake Erie and causes barefoot bathers considerable distress. Baerg (JParasit 8 86, 1922) regarded large species of *Mutilla* as the most dangerous stinging insects of the tropical forests of Peru. South American ants are the equals of wasps in the severity of their stings for *Paraponera clavata* once caused numbness and blistering and again caused a swelling 15 cm across, lasting 3 hours, in the personal experience of Weber (Sci 89 127 1929)

Hornets and wasps are the more generally feared of the Hymenoptera some of the many species are of large size and are truly formidable. Phisalix (1897) studying the venom of the common hornet found that, like that of

the honeybee it is not an albuminoid or alkaloid it is soluble in alcohol and is detoxified at 120° C., a difference from bee venom Phisalix s experiments indicated that injections of hornet venom curiously serve to immunize against vipers. A patient stung by wasps suffered a profound reaction requiring the administration of oxygen even on the fourth day when cortisone was given with apparently life-saving benefit by Williams (SoCarolMAJ 47 187 1951)

Ichneumon flies, lacking true stings, possess poison glands and various species can inflict painful wounds. From California Von Geldern (Sci 65 302, 1927) reported domestic invasion by a small proctotrupid of the genus *Epyris* occurring particularly in the fall when it gets into bedding and clothing; it stings when brushed or crushed and has been known to produce severe systemic effects.

Scleroderma domestica a 3 to 4 mm. winged, brownish insect, the larvae of which are parasites of the woodworm, caused itchy papular lesions of the forearms of a housewife who cleaned out a worm-eaten cupboard (Fuchs Dermatologica 105 213 1952)

GRANULOMAS FOLLOWING BITES AND STINGS.—See Tick bit (p 600) Scabies granuloma (p. 600); Simuliidae gnat bites (p. 633)

REPELLENTS AND INSECTICIDES.—See Dermatitis venenata repellents also Frear (Chemistry of Insecticides and Fungicides, Van Nostrand, 1942), Ldit (BMJ 1 708, 1945 1: 182, 1946) dimethyl phthalate; Horton et al. (Sci 107 246, 1948) gamma benzene hexachlorid Gammexane smear for impregnation of clothing in concentration of 2 Gm. per square foot; Dethier (Chemical Insect Attractants and Repellents Blakiston, 1948) Brown (Insect Control By Chemicals, Wiley 1951); Shepard (The Chemistry and Action of Insecticides, McGraw Hill, 1951)

BITES AND STINGS.—Phisalix (Animaux venimeux et venins, Masson, 1922) Ward (BMJ 2 702, 1939), angioneurotic edema following bee sting, successful hyposensitization; Geary (J 113 617, 1939) diabetic stung by bee needed less insulin Nobl and Hailey (MedAnnDC 10 93, 1941) severe reaction to bee, with lymphangitis Obermayer (ADS 61 390, 1945) generalized formication following bee sting; Reed (IAf MJ 23: 248, 1940) asthma from bee sting QMN (J 138 641 1948 143 1039 1950), preparation of bee antigen, extracting ground whole body of insect, and commercial sources Allen (AmJPath 24 367, 1948) cutaneous reactions to arthropodan bites, chronic lesions, histopathology Neher (J 141; 220, 1949) failure of immunization to bee Paul and Presley (HDLJ 97 282, 1950) anaphylactic reaction to wasp; Gordon (BMJ 2 237 316, 1950) various kinds of injury produced by arthropods mechanical lesions, sensitization, venomous effects and secondary infection; Goldman et al. (JID 18 403, 1952) biting parts of arthropods and lesions they produce Trice (ADS 64; 586, 1953), granulomas following bites cured by electrodesiccation; Mueller and Hill (NEngJM 249; 726, 1953), severe reactions hyposensitization to bee and wasp stings, sources of antigens Allington and Allington (J 155 240, 1954) review article, all kinds of bites and stings.

ARTHROPODS IN MEDICINE

A brief indication must suffice regarding the uses to which arthropods and their products have been put and so may be of dermatologic interest The articles of Gudger (J 84 1861 1925) Hinman (JTropM 38 128 1933) Robinson (JEconomicEntomol 30 41 1937) and Essex (PhysiolRev 25 148 1945) supply details and references. The mandibles of ants and beetles have been used to stitch wounds, a surgical technic dating into antiquity in India and common in Spain, France and Italy during the Renaissance Mosquitoes have served to transmit therapeutic malaria to paretics, maggots to clean the wounds of osteomyelitis. Xenodiagnosis consists in letting a clean vector extract and concentrate filariae from a suspected patient so that the worm is easier to find in the insect than directly in the patient s tissues. Macerated ticks have served efficiently as vaccine protecting against Rocky Mountain spotted fever A similar vaccine acts against yellow fever Silk, shellac, honey cochineal, cantharides, beeswax and spider web (styptic) are arthropod products. *Powdered cockroaches have been given in Russia as a diuretic; one* is astounded by the jumbles stews and extracts of creatures used medicinally in ancient and medieval times, as well as by those found in the homeopathic pharmacopoeia of 1882. I am not equipped to judge the utility of bee venom in the treatment of arthritis and other diseases in which favorable results have been claimed see Beck (Bee Venom Therapy Appleton-Century, 1935), and QMN (J 154 880 1954) which quoted the doubts of Kroner et al. (AnnIntM 11 1077 1938)

VERTEBRATE BITES

Venomous Bites were discussed in detail by Castellani and Chalmers (Tropical Medicine Wood, 1929) and Phisalix (Animaux venimeux et venins,

Masson, 1922) see Harmon and Pollard (Bibliography of Animal Venoms, Univ of Florida Press 1948)

VENOMOUS FISHES include the scorpion fishes rose fishes and rock cod (BullUSAMD 72 10 76 32, 1944) The lump fish a spiny creature of the tropical Pacific may even cause death Ichthyosarcotoxins are usually neurotoxins of considerable potency (Khlentzos AmJTropM 30 785 1950 Lee and Lang AmJTropM 25 281 1945 Larsen QueensHospBull 2 1 1925 Watanabe SpecSciRpt Fish, no 25 Fish and Wildlife Service 209 1950) Under study by Halstead and Bolls (Sci 119: 160 1954) whose interests were in particular the moray eel and the snapper the toxin appeared to be of small molecular size

THE STING RAY is capable of stabbing painfully with its barbed spine (Evans Sting Fish and Seafarer Faber and Faber 1943) but uneventful healing of such a wound may be expected (Bassler Sci 96 274 1942)

TOAD VENOM is alleged to have a tonic action on the heart though inferior to digitalis (Cornilleau PresseMéd 47 340 1939)

Lizard Bites.—Heloderma the Gila monster found chiefly in Arizona and New Mexico *and the beaded lizard of southwestern Mexico are the only* poisonous lizards. While the Gila monster is a sluggish creature and its anatomic construction is not conducive to the efficient introduction of venom, which is supplied through grooved lower teeth from the salivary glands rather *than through tubular upper fangs as in snakes, yet it can cause paralysis,* dyspnea and convulsions, though not likely a fatality When biting it tries to turn onto its back and it holds on hard to dislodge and chews so as to pump venom into its victim If attacked one must manage as quickly as possible to pry its jaws apart Then the use of a tourniquet obstructive only of venous flow and refrigeration with a large ice pack if available would be appropriate

Snakes of various kinds are venomous, the hollow or grooved fangs providing the passageway from venom glands to victim. Kellaway (MJAustral 2 585 1938) described the various effects *neurotoxic* with drunken incoordination, blunting of sensation increasing drowsiness, dilation of pupils, slurring of speech difficulty of swallowing slowing of respiration, coma and death preceded by convulsions and *hemolytic and cytolytic* with edema, pain, purpura salivation, vomiting blanching of skin rapid shallow respiration and cardiovascular failure leading to death and *coagulant* such that in extreme poisoning the portal and mesenteric veins and vena cava may be clotted within a few minutes.

Symptoms appear within a few seconds or minutes with nausea vomiting faintness, perhaps pain in the chest and abdomen. Albuminuria, hematuria and hemorrhages from mouth stomach and bowels may be seen.

The cottonmouth copperhead and rattlesnake are pit vipers the brightly colored coral snake is the only other poisonous snake of the U.S.A. The pupils of the pit vipers are vertical slits An adder is the only poisonous snake of England but killed only 7 persons in the past 50 years, wrote Walker (BMJ 2 13 1945) Its bite causes massive edema, pain and petechial hemorrhage, the victim being out of danger after 12 hours as a rule. Surveying cases of snake bite occurring in Virginia Wood (AmJTropM 3 936 1954) observed that most of them were inflicted by copperheads, some by timber rattlesnakes. The ratio of male to female victims was 2 1 Some 25% of the bites were sustained by children 8 years old or younger The lower extremity was the usual site Upper extremity bites were twice as frequently fatal, statistically as lower extremity bites, and bites on the head or trunk were more dangerous than those on the hands or arms.

One cannot recognize the identity of the snake from the symptoms, which vary greatly depending on the dose of venom received, Kellaway stated. One notes the distance between the punctures as indicative of the size of the snake One distinguishes the snap bite from the hold-on type The pit vipers of the

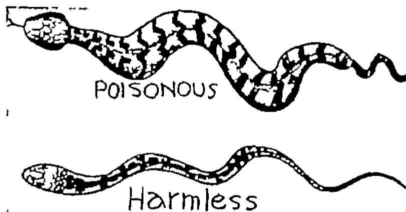
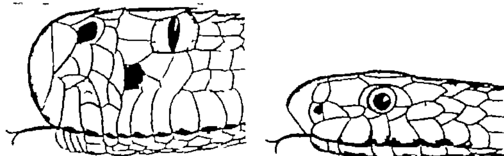


Fig. 866.—Top diagram *Poisonous snake*, with lance-shaped head, narrow neck, short, thick body and definite tail. Lower diagram *Harmless snake* with head, neck and body of nearly the same diameters and with no definite junction between the body and the tail. (Dr J W Pender PSMMC 18 743, 1940.)



Figs. 867 and 868.—Left *Poisonous snake* of pit viper group, lateral view of head, showing oval pupil and pit Right *Harmless snake* lateral view of head showing round pupil and no pit. (Dr J W Pender)

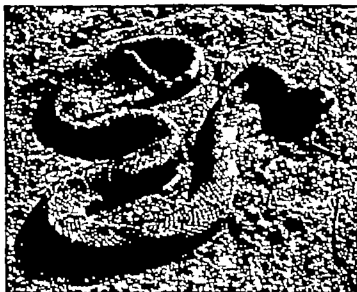


Fig. 869.—*Crotalus atrox* (Baird and Girard), the desert diamond rattlesnake. (Photograph, National Park Service, from Merck Report, July 1940, article by Herbert L. Stahnke Some Poisonous Animals of the United States, by permission of the author and publisher; from Gradwohl et al. Clinical Tropical Medicine Mosby 1951.)

United States leave 2 small puncture wounds. The thickness of clothing or absence thereof at the site is significant. A chance intravenous injection of venom is rapidly fatal.

Histologic lesions resulting from snake bite have been studied by Amorim et al. (J 15? 50 1953); experimental animals showed severe hemorrhage and edema with coagulation necrosis of subcutaneous tissue and muscles at the site of injection of the venom of Bothrops. In poisoning by Crotalus such lesions were rarely present in internal organs, but were found in the nervous system. Injections of bothropic venom often caused hyaline thrombosis of the capillaries, but crotalic venom did not and hemorrhagic glomerular lesions of the kidneys were caused by the former but not by the latter. Variations in pathologic findings depended not only on the kind of venom but also on the kind of animal upon which it acted.

TREATMENT OF SNAKE BITE.—Lender (USMMC 1? 743 1940) urged the application of a tourniquet an inch or two proximal to the wound prior to investigating the type of snake. The tourniquet should obstruct venous but not arterial flow. Crisscross incisions should be made through each fang mark, allowing free bleeding and suction should be applied to these for at least half an hour. The tourniquet should be loosened for 1 minute of each 20 and may be moved proximally as the swelling increases. Antivenin is the best and surest measure when the specific type is promptly available according to Allen (SouthMJ 31 1248 1938 AmJTropM 19: 393 1939) who believed that the tourniquet is harmful rather than helpful, and that timid incision is practically useless while excision as for carbuncle or even amputation may be requisite to save life.

Antivenin saves some victims of the bite of the Indian krait symptoms of which are colubrine with salivation coldness and prostration but without swelling or pain (D Abreu IndMGaz 74 94 1939).

Refrigeration (see Scorpion sting) is of debated value strongly recommended by Allen (SouthMJ 31 1248 1938 AmJSurg 68 170 1945 J 151 1156 1953). It probably does effect a therapeutically consequential delay of absorption of venom and its use does not prevent the use also of incision and suction, and the venous tourniquet. Its symptomatic value in allaying the medically trivial bites and stings cannot be denied.

Cortisone and ACTH used in the treatment of 3 cases of snake bite notably decreased morbidity reported Hoback and Green (J 152 236 1953) an observation confirmed by the more extensive experience and the experimental data recorded by Wood et al (VaMMonth 82 130 1955).

USES OF SNAKE VENOM.—Cobra venom may be used therapeutically for the relief of pain in doses of 5 M. U. Analgesia is slower but more lasting than that from morphine (Macht MP&Circ 201 254 1939 UCutRev 44 119 1940). It is of value in the palliation of advanced carcinoma (Maier MWorld 57 181 1939). Peck et al (ADS 35 831 1937) discussed the use of moccasin venom in the treatment of purpura. Venom of the tiger snake may be used topically to secure hemostasis a dilution of 1 10 being capable of clotting citrated or oxalated blood (Rosenfeld and Lenke AmJMedSci 190 779 1935).

See Jackson (SouthMJ 22 605, 1929) Jackson and Harrison (J 90 1928, 1929) Cawston (JTropM 42 97 1939) African snakes Stanley Jones and Harris (HIJ 21 [illegible] 1943) adder bite purpura and 1 month morbidity, Nauss (Medical Parasitology and Zoology Hoeber 1944) poisonous snakes Chotkowski (NEngJM 241 606 1949), poisonous snakes of New England Ortenburger (OklaSMAJ 45 211 1952) Borges (Sci 117 47 1953) snake venom chemistry.

Crocodiles let go if the eyes are gouged (De Hartogh JTropM 44 112, 1941).

Canine and Other Bites liable to inoculate rabies should be irrigated at once and profusely with 20% soft soap solution, which is as effective as the obsolete treatment with nitric acid according to Shaughnessy and Zichis (J 123 528, 1943). The wound is dealt with according to ordinary surgical principles. The animal, however must be secured and kept captive in isolation

for a week to determine whether it is rabid; one does *not* destroy the animal until certainty is reached regarding whether it does or does not harbor disease. Rabies has been inoculated by the bites of bats (Kough: J 155 441, 1954)

In addition to standard antirabies vaccination which must be undertaken immediately if the possibility of rabies inoculation exists, one may secure antibodies immediately by the use of Koprowski's antiserum, which is made by injecting into the horse large doses of rabies vaccine over a long period of time When the bite is on or near the face and a short incubation period is expected, the use of this serum aids in establishing early immunity (QMN J 157 1458 1955)

Rat or cat bites may inoculate rat bite fever (q v) A *Pasteurella* infection with local and regional abscess formation and prolonged convalescence following cat bites was described by Allin (CanadMAJ 46 48 1942) See Hull (Diseases Transmitted From Animals to Man Thomas 1941) also cat scratch disease.

Penicillin appeared to prevent serious difficulties following mauling by a lion, reported Kemp (J 137 22 1948) for such injuries, traumatizing enough uncomplicated, are generally infected with an assortment of pathogenic bacteria.

Human Bites assume medical importance because of infection which may occur in them from mouth organisms. Most cases result from fights or erotic agitation, but Butterworth (ADS 35 1162, 1937) called attention to those self inflicted by idiots, whose hands as a result show arciform hypertrophic and atrophic scars. In management, Maier (AnnSurg 106 423 1937) advised débridement, the operator alert to the possibility of injury to tendons. Liability to Vincent's infection requires early radical treatment, according to McMaster (AmJSurg 45 60, 1939) The wound is likely to be a small, jagged sore over the knuckle with swelling of the hand cellulitis and foul discharge when seen on the third or fourth day (Cohn Surg 7: 546 1940) Virulent destruction, ankylosis, or amputation may succeed upon a seemingly trivial wound (Boland J 116 127 1941) Speirs (SGO 72: 619 1941) discussing 114 cases, advised gentle but thorough cleansing with soap débridement only of damaged tissue, the avoidance of cauterization, excision, or the use of strong agents, and the application of a dry sterile dressing. Probing and suturing are not advisable (Miller and Winfield SGO 74 153 1942) A suitable antibiotic should be given for a few days, and serologic tests should be done monthly for several months so that syphilis, if inoculated, will be recognized.

See Boyce (SouthMJ 35 631 1942), 90 cases Henry (MilSurg 97 132, 1945) 2 cases, Boyce (SouthSurg 14: 690 1948) 120 bites in 93 persons, 70 affecting hand; Cruikshank and Bates (AmJSurg 80 646, 1950) head and neck cases not as bad as those of hand; Levin and Longacre (J 147 815, 1951) 27 cases, good results with sulfonamides and penicillin.

DERMATOSES DUE TO METABOLIC DISORDER

XANTHOMA

Xanthomas are disturbances of lipid metabolism resulting in the deposition of oily substances in and between the cells of tissues, including those of the skin. The deposits, discrete or diffuse, have a yellowish hue.

Fatty Substances Occurring in the Human Body (Aschoff, Lectures on Pathology, Hoeber 1924) are:

1. Nitrogen-free, phosphorus-free lipid, including:
   a. neutral fats, which are glycerol esters with fatty acids.
   b. fatty acids and Na, K, Ca soaps formed from them (oleic, palmitic, stearic);
   c. cholesterin, a monatomic alcohol $C_{27}H_{45}OH$, which may occur free or in esters.
   d. cholesterin fat, combinations of cholesterin and fatty acids.
2. Phosphatides, which contain N and P and comprise esters of orthophosphoric acid, including lecithin and cephalin, which are unsaturated, and sphingomyelin, which is saturated.
   a. lecithin is the monoamino-monophosphatide-stearyl-oleyl-glycerophosphate of choline;
   b. cephalin is a monoamino-monophosphatide differing from lecithin in having an amino alcohol in place of choline, extractable by ether;
   c. *sphingomyelin* is *a diamino-monophosphatide which yields on hydrolysis phosphoric* acid, choline, a fatty acid, and sphingosine, a base, le amino alcohol, not extractable by ether.
3. Cerebrosides, containing N but lacking P, which comprise glycolipins, including the galactosides cerasine and phrenosin.
4. Lipochromes and other fat-containing pigment, such as carotinoids and lipofuscin.

Fractional Extraction of Lipids (Lawmon, ADS 35: 460 1937)

Acetone { extract neutral fat, cholesterol and its esters, acetone-soluble phosphatides, fatty acid; leaves unsaturated and saturated phosphatides, and cerebrosides;

Ether { extract unsaturated phosphatides; leaves saturated phosphatides and cerebrosides;

Alcohol (absolute) dissolves saturated phosphatides and cerebrosides.

Normal Values for Blood Lipids, following Montgomery (JID 1 323 1939) are in milligrams per 100 cc of plasma: total cholesterol, 160-200; cholesterol esters, 110-145; lecithin, 200-230; total fatty acids, 335-350; and total lipids, 500-530. Averaged and expressed as a percentage of the total lipids: total cholesterol, 34% (cholesterol esters 70% of the total cholesterol), lecithin 43%, and total fatty acids 66%. Approximate values for lipid content of normal skin (epidermis and cutis, excluding the subcutaneous layer) are: total lipids, less than 3% of the wet weight of the tissue (based on immediate analysis of adequately large specimens); total cholesterol, traces to 13% of the total lipids; and lecithin, traces to 30% of the total lipids. Lecithin determinations in either blood or tissue have occasionally exceeded the total fatty acids of which they are a part, as a result of different methods of analysis. There is no variation in normal lipid content of the blood with different ages. Moderate elevation of blood lipids is found in obesity and in patients with low basal metabolic rates. Cholesterol tolerance tests and determinations of iodine number, concerned with the degree of unsaturation of the fatty acids, are apparently of little value in studying cutaneous xanthoma or other dermatoses. It is desirable to make complete and, if possible, multiple determinations of all blood plasma lipids. While the blood cholesterol may be normal, yet there may be a marked increase in other lipids, or there may be a significant imbalance between the various lipids.

The normal range of serum lipids is wide (Page et al., J Biol Chem 111 613, 1935) and in diabetes there was no relation between the blood cholesterol and the severity of diabetes, dietary fat or degree of accompanying arteriosclerosis (Man and Peters, J Clin I v 13 237 1934).

In normal persons, overdosage of fat by oral ingestion of from 1 to ... gm./kg. resulted in an increase of blood lipid which reached a maximum after 3 hours and fell to normal from 6 to 9 hours; in diabetics the increase was greater and more prolonged (Hatakeyama et al., Biochem Ztschr 300 302, 1939). The change involved largely the neutral fats and phosphatides, while the free and esterified cholesterol concentration remained almost unchanged. The cholesterol tolerance test of Bürger was described by Bloch (BJD 43: 70 1931). It is not of great practical value.

The lipids of animals and plants were fully discussed by *Deuel* (*The Lipids, Their Chemistry and Biochemistry*, Interscience Publishers, Vol. I, 1951; Vol. II 1955).

Lipid Metabolism is related of course to ingestion, for diets differ widely in chemical composition. It is related to thyroid function, for in hypothyroidism hyperlipemia exists and in hyperthyroidism hypolipemia exists in myxedematous xanthoma cases, thyroid may bring about involution (Sweitzer and Winer ADS 42 419 1940 Curtis and Blaylock ADS 66 460 1952) It is related to pancreatic function for many diabetics are hyperlipemic and lipocaic (a pancreatic hormone lacking which a depancreatized dog dies of fatty degeneration of the liver within 3 months despite insulin therapy) is concerned (Dragstedt et al. AIntM 64 1017 1939) It is doubtless related to other hormones and functions which are not as yet understood for cortisone too reduces hyperlipemia

Metabolic mechanisms are inherited to a greater or lesser extent Xanthoma tuberosum is seen in some individuals with essential familial hypercholesterolemia Four generations, for example of a family studied by Wilkinson et al. (AnnIntM 29 621, 1948) contained 282 persons, of whom 169 were examined and it was found that if 1 parent had elevated blood cholesterol, half of his children showed this, while if neither parent had it the children were all normal In 1 group both parents were hypercholesterolemic and 6 of their 18 children had lesions of xanthoma tuberosum No relation was found between ingestion of cholesterol and blood levels in either normal or abnormal individuals.

Serum lipids are transported in the main by the serum lipoproteins. The most severe defects found in studies of lipoproteins by high speed centrifugation methods were found in the serums of patients with primary familial lipidoses with xanthoma tuberosum (McGinley et al. JID 19 71 1952) There was marked increase in the concentration of the S_f 10-20 and 20-40 classes of lipoproteins, which are the ones also associated with atherosclerosis.

Classification of Xanthoma.—A good working tabulation is that of McGinley et al. (JID 19 71 1952) who commented that differentiation is made on clinical pathologic and chemical evidence separating the primary diseases of the reticulo-endothelial system from those in which an error in lipid metabolism appears to be primary In addition to their groups I and II they called attention to miscellaneous conditions showing foam cells in cutaneous lesions, but not true xanthomas and so not listed in the table

I. Primary reticulo-endothelial disease with xanthoma
- Letterer-Siwe disease
- Hand-Schüller-Christian disease
- Eosinophilic granuloma
- Xanthoma disseminata
- Nevoxanthoendothelioma (juvenile xanthoma)
- (All of the above are probably variants of the same disease process.)

II. Lipidoses associated with xanthoma
- A Primary familial lipidoses
  - Xanthoma of plane or tuberous type
  - Xanthoma of tendon sheaths
  - Familial xanthoma with high familial incidence of cardiovascular disease and hypercholesteremia
  - Xanthoma with high incidence of atherosclerotic cardiovascular disease
  - Xanthelasma (?)
  - (These [illegible] may exist singly or in any combination.)
- B Secondary lipidoses with xanthoma
  - Primary biliary cirrhosis
  - Obstructive biliary disease
  - Chronic pancreatitis
  - Diabetes
  - Myxedema
  - Idiopathic hyperlipemia with hepatosplenomegaly (position of which syndrome is unsettled)

See Urbach (Lipoidstoffwechselerkrankungen der Haut, Handb. J. Springer, 12 2, 230, 1932 [illegible] 1934 p 241) Wehlme (AIM 48 [illegible] 1937); Montgomery and Osterberg (ADS 37 374 1938) [illegible] cases The latter and Magnusson (AnnIntM 11 [illegible] 1938) [illegible] review with bibliography Montgomery (AnnIntM 13 671, 1939) classification and exemplary cases (MCl N Am 24 1249, 1940) lipid metabolism O'Leary and Montgomery (Canad MAJ 57 448, 1947) review photographs Thannhauser (Lipidoses, Diseases of the Cellular Lipid Metabolism, ed. 2, Oxford University Press, 1950 [illegible] pp 125 illustr)

Types of Cutaneous Involvement.—Two are recognized: (1) **Xanthoma Tuberosum**, which is characterized by lesions predominantly on extensor surfaces, hyperlipemia and frequent association with severe cardiovascular disease especially angina pectoris and (2) **Xanthoma Disseminatum**, which is characterized by lesions predominantly on flexural surfaces and also mucous membranes, including those of the mouth pharynx and larynx blood lipid levels within normal limits, and frequent association with diabetes insipidus.

Eruptive xanthoma occurring in lipemia is a symptom thereof and is seen in diabetes mellitus and xanthomatous biliary cirrhosis (Wilder AmIntM 61 207 1938). Essential xanthomatosis may or may not be accompanied by hypercholesterolemia. With hypercholesterolemia the skin lesion is basically nodular and involvement of the tendons, tendon sheaths, blood vessels and bile ducts, with secondary biliary cirrhosis, may take place. Without hypercholesterolemia the lesions are generally finely papular and confluent or actually diffuse although nodules may form in the membranous bones as in Hand-Schüller-Christian disease. Combined types occur see Montgomery and Osterberg (PSMMC 12 641 1937). Even marked lipemia will not damage reticular cells unless these are originally defective Wilder thought. The lesions may occasionally be papulopustular. They contain neutral fat fatty acids cholesterol and other lipids. Hyperlipemia and the diabetic sugar tolerance curve may be detected by studies of the chemistry of the blood. Recovery is the rule and can be hastened by control of the diabetes, if it is present which should be accomplished with the generous use of insulin and a diet not too rich in fats. Low fat diet and thyroid are likely to be helpful.

Xanthoma Tuberosum.—The lesions are widely disseminated and the eruption, which is more or less generalized in character may consist of papules, tubercles nodules and even tumors, often intermixed with plaques and striae. The sites of predilection are the elbows, hips and knees although no region is exempt. On the palms and soles the lesions, because of their peculiar saffron color stand out in bold relief. Rarely the nodules coalesce forming tumors several centimeters in diameter. Their consistency ranges considerably but as a rule they are firm. They develop slowly and seldom involute although spontaneous regression has been noted. Mucous membranes may be attacked

Familial prevalence occurs. A father and daughter were reported by Lane and Goodman (ADS 3? 377 1935) and 5 cases in 1 family by Levin and Sullivan (ADS 34 ?? 1936). An extensive genealogic study of familial hypercholesteremia by Fliegelman et al (ADS 58 409 1948) suggested that transmission occurs as an incomplete dominant; xanthoma tuberosum represents the homozygous state for the inherited factor which when heterozygous produces only hypercholesteremia, while the mating of two heterozygotes may result in xanthoma tuberosum. See Hornerup's monograph (J 143 935, 1930).

The lesion may attain remarkable size (Swanson BJD 55; ?? 1943). Grotesque involvement of the face was observed in a woman of 50 (Strandberg: ActaD-V 1? 466, 1936). Involvement of the cornea was the unusual feature in a patient presented by Rattner et al. (ADS 59 510 1949) and the blood total cholesterol attained a level of 1,200 mg per cent.

Xanthomas are not limited to cutaneous distribution, but occur within joints as pedunculated tumors attached to the synovial membrane usually of the knee (DeSanto and Wilson JBJSurg 1? 531 1939) causing pain, stiffness and nonmalignant tumor. Tendon sheath and synovial membrane cases were collated by Galloway et al. (ArchSurg 40 485, 1940); the lesions were of slow growth firm and nontender occurring in feet, ankles and hands at about age 40 the location sometimes being determined by trauma. About 10% recurred after excision. Dupuytren's contracture, affecting the medial palmar fascia and causing scarlike flexion of the fifth finger is possibly of xanthomatous nature (Meyerding et al SGO 7? 88 1941).

Resorption Xanthomas comprise processes described as degenerative or inflammatory cholesterosis where the xanthoma formation is local and the lipids, freed locally are stored there by lymphocytic or connective tissue cells. This has been observed in the scars of syphilitic gummas, laparotomy wounds and herpes zoster (Anderson ADS 48 471 1943 49 140 1944 Netherton ADS 51 100 1945). The development of xanthomas in scars was reviewed by Weidman and Boston (AmIntM 9 793 1937). Their patients showed lesions in the cicatrices following herpes zoster and they found a dozen cases of







Fig. 870.—Tuberose xanthoma. (Dr F. S. Burns.)
Fig. 871.—Xanthoma nodules in skin of thumb.
Fig. 872.—Tuberose xanthoma of elbow. (Dr F. G. Harris.)



Fig. 873.—Xanthoma tuberosum multiplex. (Dr Clyde L. Cummer.)



Fig. 874.—Eruptive xanthoma, typical lesions of knees. (Dr T. C. Gilchrist.)



Fig. 875.—Xanthoma tuberosum overlying interphalangeal joints. (Dr Anstruther Davidson.)

scar xanthoma in the literature see Kreibich (AfDuS 152 365 1926) A case manifesting curious chronic fat-containing nodules on the extremities was described by Urbach and Hill (ADS 41 180 1940) as lipid imbibition of degenerated collagenous tissue

Juvenile Xanthoma (Nevoxanthoendothelioma)—Tuberose xanthoma in infants was reported by McDonagh (BJD 24 85 1912) In the patient of Lamb and Lain (SMJ 30 585 1937) the lesions involuted as the years passed and on the scalp produced permanent striking alopecia. Such cases are notable for the remarkable clinical appearance of the coppery or lemon-colored papules, nodules and tumors, which are usually more pronounced on the upper half of the body The patient s health is little affected although the blood cholesterol and total lipid are much increased according to Zeisler (ADS 40 626 1939) normal according to Nomland (JID 22 207, 1954) These tuberous xanthomas in children are occasionally solitary Their firm, rounded, orange-colored noninflammatory nodular character distinguishes them from other tumors (Charache AmJCanc 31 563 1937 Fichman AmJSurg 48 456 1940)

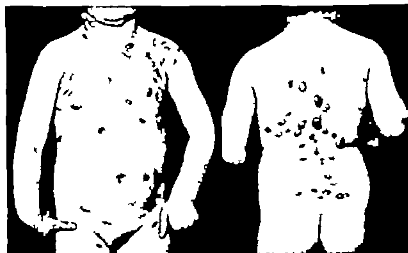


Fig 8 6—Juvenile tuberose xanthoma. (Lamb and Lain SouthMJ 30 585, 1937)

That these lesions are xanthomas, not nevi or endotheliomas, was the convincing argument of Senear and Caro (ADS 34 195 1936) They are likely to resorb spontaneously if one is patient and in the scalp generally leave a patch of alopecia

The onset was at age 6 weeks in the 7 year-old patient presented by Oliver (ADS 39 576 1939) and at 6 months in the girl exhibited at age 2 by Allington (ADS 36 663 1937) The Negro infant of Blank et al. (Ped 4 349 1949) had 1 of his tumors in the ciliary body and the eye was enucleated See Rattner et al (ADS 58 484 1948) and Lavmon and Schoch (MinnM 32 596 1949) Perhaps Turner referred to a case attributing it to prenatal influences in his Treatise of Diseases Incident to the Skin (London, 1726 p 179)

Xanthoma Diabeticorum is eruptive tuberous xanthoma when it occurs in cases of diabetes mellitus (Combes and Behrman ADS 43 927 1941) The lesions exhibit a predilection for the buttocks elbows and knees. They are firm solid rounded reddish yellow papules, from 0.5 to 1 0 cm in diameter The lesions may be asymptomatic itchy or painful They develop suddenly While generally discrete and few in number they may be numerous. After persisting for several months, or years, the papules may disappear spontaneously leaving no trace. Relapses are of fairly common occurrence The patients are usually overweight and of middle age The location of the lesions is influenced by trauma (Sugg and Stetson J 109 414, 1937) Some 90%

of the cases occur in females and affect individuals between the ages of 20 and 45 years (Thompson et al. SouthMJ 28 895 1935) Bizarro linear criss-crossing keloid like lesions were observed in a Negress, aged 34 studied by Wise and Garb (ADS 45 723 1942)

Xanthomas in diabetics regress usually without a trace and fairly promptly on treatment directed against hyperlipemia (Garb AnnIntM 19 241 1943) but fatty diet did not alter the blood cholesterol in 27 diabetic patients studied by Wilder (AIntM 57 434 1936) In uncontrolled diabetes with hyper cholesteremia and xanthoma, the control of diabetes may be expected to di



Fig. 377—Eruptive xanthoma in a diabetic.



Fig. 378—Eruptive xanthoma in a diabetic. (Dr Philip F Shaffner)

minish lipemia (Finnerty RevGastroent 7 166 1940) The serum is milky with neutral fat in these cases but in xanthoma tuberosum the serum is usu ally not milky for neutral fat is only slightly increased, although cholesterol and its esters are elevated.

The acute onset and clinical appearance of the eruption simulated xan thoma occurring in diabetes in the case of Frank and Levitt (ADS 64 434 1951) but the carbohydrate tolerance was normal, and the rash disappeared within 7 months following dietary treatment only

Xanthoma Palpebrarum (Xanthelasma) consists of rounded yellowish infiltrations in the skin of 1 or both lids of 1 or both eyes. Women are more often affected than men. The lesions develop slowly during middle age or

later years and are at all times soft, noninflammatory and practically asymptomatic. Palpebral involvement is said to be frequently associated with the other forms of tuberous xanthomatosis, and moderate hyperlipemia occurs in about 70% of the patients (Curtis ADS 55 507 1947). Abnormal cholesterol distribution on chemical fractionation of the lyophilized serum was found in the majority of the cases of Fowlkes and Forbes (ADS 62 681 1950) who administered a pancreatin preparation with variable results on the quantity of the readily extractable fraction. Association with cardiovascular disease is not unusual. It was especially conspicuous in the family studied by McKinney (BMJ 2 1259 1950): 9 of 11 offspring carrying xanthoma as a dominant trait died cardiovascular deaths.



Fig. 3 8.—Xanthelasma.



Fig. 339.—Xanthoma affecting cornea as well as skin. (Rattner ADS 38 510 1938.)

The lesions may be excised or neglected or one can destroy them by means of cautery or solid carbon dioxide. The scar of the cautery burn does not contract but it may be depigmented. The cautery treatment was described by Wallhauser (JCutD 35 593 1917). Monopolar electrodesiccation may be used successfully (Silvers J 105 796 1935). Vitamin B injections in doses of 500 μg weekly were followed by flattening of the lesions in 6 weeks, reported Robinson (JID 24 111 1955).

Extracellular Cholesterosis.—The first patient (Urbach et al. AfDuS 166 248 1932, DZtschr 66 371 1933, YBD 1934 p 241) was an old woman who had progressively enlarging reddish blue nodules on the dorsum of the hands, soon also on the arms, later on the knees, thighs, ears and tongue, and finally scattered over the chest, arms and buttocks in violet patches and xanthic papules. There were also hypertension and cardiac decompensation, and the spleen and liver were enlarged and firm. The case reported by Laymon (ADS 35 269 1937) involved a girl of 16 whose eruption began at the age of 5 years with vesicles which became papules. Some small lesions seemed to

coalesce especially on the backs of the hands, the knees and about the ankles. Brownish violet mottled pigmentation, atrophy and scarring developed scattered over the buttocks, thighs and legs. The histologic and chemical findings were those of extracellular cholesterosis, foam cells and giant cells being absent. A man who developed extensive cutaneous lesions histologically compatible with the diagnosis of extracellular cholesterosis proved to have retroperitoneal lymphosarcoma at autopsy (Frost and Anderson, ADS 39: 1061, 1939). A woman whose eruption developed during pregnancy showed typical features of Urbach's disease and in addition suffered pulmonary involvement (Sobel and Pollock, ADS 58: 206, 1948); she was not hyperlipemic.



Fig. 341.—Extracellular (nodular) xanthoma. (Laymon, ADS 35: 203, 1937.)



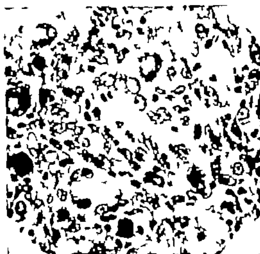


Fig. 342.—Hand-Schüller-Christian syndrome. See Fig. 343. (Horsfall and Smith, Quart J M 4: 37, 1934.)

Fig. 343.—Hand-Schüller-Christian syndrome. Histologic structure of lesions of the patient shown in Fig. 342. The granulomas are composed of large pale-staining cells with foamy lipid-filled cytoplasm and vesicular nuclei as well as many multinucleated giant cells, also containing lipid.

Hand-Schüller-Christian Syndrome.—The first recorded patient with the combination of defects of the membranous bones, exophthalmos and diabetes insipidus was that of Hand (APed 10: 673, 1893). Arrest of development leading to dwarfism is an additional feature, Atkinson (BritJChildDis 34: 28, 1937) judged from his survey of 103 cases. All the features of the disease need not be, and generally are not, present in a particular case, and symptoms and signs vary according to the situation of the lesions.

Defects of the cranial bones are an almost constant finding, while exophthalmos and diabetes insipidus are less constant. Diagnosis is made, Atkinson stated, by clinical picture, histologic examination and roentgenograms, which alone may be distinctive, but changed blood lipid levels are not diagnostically requisite. Yellow infiltrations of skin, mucosae, serosae, tendon

sheaths and fascia along with infiltrations and nodules in liver spleen lungs, heart lymph nodes marrow and glands of internal secretion were observed by Lane and Smith (ADS 39 617 1939) who listed cutaneous manifestations as including bronze pigmentation, maculopustular and hemorrhagic eruptions, and seborrhea like involvement of the lids.

The primary pathologic lesion is composed of reticulo-endothelial cells, singly or multiply nucleated filled with lipid along with foreign body giant cells, eosinophils round cells and young fibrous connective tissue cells. Old lesions are composed mainly of foreign body giant cells, fibrous tissue necrotic tissue and cholesterol crystals. While in Gaucher's disease the lipid improperly metabolized is a kerasin and in Niemann Pick's disease a lecithin, in this condition it is a cholesterin compound (Wahl J 107 422, 1936)

Some benefit has been obtained with dietary treatment pituitary extract and x ray treatment (Kennedy PSMDMC 13: 776 1938) In some 30% of the cases the disease has proved fatal

As there are infantile and adult forms of Gaucher's disease and of Niemann Pick's disease with rather marked clinical difference of behavior so there appear to be infantile and adult forms of Hand-Schüller-Christian disease of which the infantile form may be the Letterer-Siwe disease. Interrelations of these reticulo-endothelioses, which include also eosinophilic xanthomatous granuloma of the bones were suggested by studies of Sweitzer et al. (ADS 40: 192, 1939) on a young boy with scattered red brown papules, malaise anorexia weight loss and nodules in the liver and bone marrow Layman and Sevenants (ADS 57: 873 1949) noted the rapid fatality in Letterer-Siwe disease with its hemorrhagic and nonlipid-containing lesions in contrast with the papular eruptions, chronicity and lipid-containing lesions of Hand-Schuller-Christian disease. It may be that Hand-Schüller-Christian disease, Letterer-Siwe disease and some eosinophilic granulomas (q v) are various phases of a disordered reticulo-endothelial system.

See Christian (MedClinNoAm 3 849 1919 Contrib to Med. & Biol. Research, Hoeber 1 390, 1919) Howland (AIntM 42 611 1928) 2 cases, 1 autopsy, review of 12 cases Horsfall and Smith (QuartJM 4 37 1935), analysis of 36 cases Wortis et al (AmJDisChild 51 353 1936) 3 cases, Strong (J 107 422, 1936) Wallgren (AmJDisChild 60 471, 1940), related diseases Cornbleet and Barnes (ADS 44 48, 1941) urinary ketosteroids in HSC case Burckhardt (Dermatologia 86 250 1942), tiny yellow nodules and petechiae in young patient Schuknecht and Perlman (AnnOtol 57, 643, 1948) temporal bone involvement; Blanchard and Boone (AmJDisChild 76 1, 1948) Wallace (AmJRoentg 62 189, 1949) Hansen (ActaRadiol 32 89 1949) related diseases.

Gaucher's Disease ("Large-Celled" Splenomegaly Cerebroside Histiocytosis) is characterized by occurrence in children familial tendency and insidious onset with anemia and xanthomatous (kerasin) splenomegaly hepatomegaly and bone marrow changes. Hemorrhages sometimes occur The skin gradually develops a even brownish, melanin pigmentation which may be symmetric but xanthomas do not develop in it Pingueculae are usual accompaniments. Lipid deposits in the bones may be found on x ray examination. A chronic course leading to death is to be expected, yet the existence of the disease does not necessitate the termination of pregnancy in an affected woman (Bromberg et al.: BMJ 761 1953)

See K lm (ActaD-V 17 600 1936) 3 cases with skin changes; Milamed and Chester (AIntM 61 798, 1938) case in male 20 Groen and Garrer (Blood 3 1221, 1948) 9 adult cases with spleen, liver lymph node and bone changes, Morrison and Hack (AmJPath 25 597 1949) histochemical studies, Stransky and Dauis-Lawas (AmJDisChild 78 494 1949) heredity in infantile type Gordon (AmJMed 8 332, 1950) osseous forms Squires et al (CanadMAJ 62 1 8, 1950) adult form, Herndon and Bender (AmJHumGenetics 2 49, 1950) 5 Negro siblings Halliday (PSExpBiol 75 689 1950) cerebrosides Hatch et al (Med 30 1 1951) review of 20 cases

Niemann Pick Disease (Phosphatide Histiocytosis) is a rare splenomegalic lipidosis of infancy occurring generally in Jewish individuals. It is characterized by brownish melanin pigmentation of the skin, malnutrition retarded development hepatosplenomegaly of pronounced degree decreased fragility of the red blood cells, leukocytosis of 20,000 to 40,000 and enormous accumulations especially of sphingomyelin in the reticulo endothelium of the parenchymatous organs and lymphoid system. The course is eventually fatal, sometimes acutely, regularly within the first years (Pick: AmJMedSci 185 601 1933) The skin is wrinkled pale and sweaty and subcutaneous fat disappears. Mucosae show diffuse and patchy pigmentation (Wiener Skin Manifestations of Internal Disorders, Mosby 194 p 466)

An adult form of Niemann Pick's disease is recognized by Thannhauser (Lipidoses, Oxford University Press 1950) The adult and infantile forms differ ... do th adult ... infantile form of ... disease In infants the course terminates in early death, but spectacular complaints are not manifested in adults, who are likely to be unaware they are diseased until enlargement of the spleen happens to be discovered. A high red cell count is likely to accompany the splenomegaly suggesting polycythemia, and pulmonary involvement was the cause of death in brothers affected.

Skin and Mucous Membrane Lipidosis With Hepatosplenomegaly was described on the basis of 1 case a boy of 11 who had small, firm, yellow nodules on the face and extremities present since birth. Histochemical changes differ from those found in lipid proteinosis, which this condition closely resembles. Differences from the Niemann Pick disease are not great. There is tremendous hyperlipemia, with or without jaundice, along with lesions present on the mucous membranes which must be distinguished from those of xanthoma disseminatum. There is frequently marked increase in free cholesterol and also in lecithin, in both the blood and tissue lipids (Urbach: KlinWchn 13 577 1934)

Letterer-Siwe Disease, a lipid reticulo-endotheliosis related to the Schüller-Christian syndrome is characterized by granulomatous proliferation of the reticulo endothelial cells, which become filled with cholesterol. Infants are affected and the disease may run a rapidly fatal course with hemorrhages and progressive enlargement of the lymph nodes, liver and bone marrow. In older persons the course is slower and the granulomas which develop tend to involve the skull, orbital bones, spleen and liver (Abt and Denenholz: AmJDisChild 51: 499 1936) The case described by Cole (ADS 56: 192, 1947) was a male born with petechiae whose skin developed brownish pigmentation and crusted and bullous lesions. The spleen and liver were hard and enlarged the abdomen tender and distended and the clotting time prolonged. The eruption was mainly on the trunk comprising telangiectases, scattered papulosquamous lesions, small vesicles, crusted areas and scars. Death ensued after severe sickness with high fever and the major manifestations of hepatosplenomegaly Anemia, purpura and hepatosplenomegaly were the clinical features, and proliferation of large pale, reticulo-endothelial cells invading and replacing the tissues of the spleen, liver bone marrow skin and lymph nodes was the histologic feature in the fatal case of Sweitzer and Laymon (ADS 59: 549 1949)

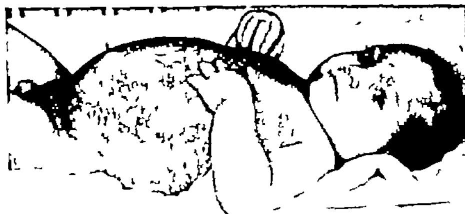


Fig. 384 —Letterer-Siwe disease The baby died. (Dr Herbert Wenner)

Some improvement ensued when ACTH was given to the patient of Bremers et al. (ADS 66: 291 1952) An apparent cure was obtained with streptomycin in an infant who underwent splenectomy with arrest of hemorrhages; when the antibiotic was used, fever and lymphadenopathy receded, petechiae stopped forming and the child remained well fo years (Aronson: Lancet 1 689 1951) Terramycin and chloramphenicol were recommended by Fisher (JB&JSurg 35-A: 445, 1953) whose patient, a child with multiple bony lesions, was the fifth in 3 years to be cured by antibiotics.

See Letterer (ZischrPath 30 377 1924) Siwe (ZischrKinderh 55 212, 1933); Teicher (ADS 67 434 1953) onset followed sulfonamide therapy of tonsillitis.

Leukemic Xanthomatosis.—A 2-year-old Puerto Rican boy developed xanthomatous lesions and subsequently a chronic leukemic myeloid response (Freud et al.: AmJDisChild 85 42, 1954) Death with leukemia followed in about 2 years. Necropsy revealed that the lymph nodes, spleen, liver lungs and many the viscera were affected by a widespread reticuloendotheliosis wherein were found many primitive mesenchymal cells that were foamy with high cholesterol content.

Lipid Degeneration of the Elastin (Cutis Rhomboidalis Nuchae)—In persons whose occupation has long exposed them to the atmosphere and actinic influences, the weathered skin may become furrowed and divided into rhomboidal and angulated fields, the texture thickened and the color pale yellow or brownish. These changes, characteristically involving the sides and back of the neck, may extend over the cheeks and upper chest and may affect the dorsa of the hands and forearms. While the changes are diffuse they are not necessarily uniform: occasionally a nodular translucent, sometimes eroded

lesion is seen, easy to confuse clinically with basal cell carcinoma. Colloid degeneration of the conjunctiva is a frequent concomitant (Kogoj abs ADS 53 297 1946) The disease was interpreted as a primary degeneration of the elastic tissue by Urbach (Actal) V 1 69 1944)

Histologic studies by Percival et al (BJD 61 269 1949) showed that the collagen bundles were greatly increased in length and underwent physical chemical changes with alteration of staining reaction and fatty degeneration or imbibition of fat in the fibers. Unique argyrophile fibers, seemingly developing from the intercollagenous ground substances rather than from reticulum or fibroblastic cells, became coarse and the abnormal collagen, with staining affinities simulating those of elastic tissue became collacin.

The skin is vulnerable and purpura may follow mild trauma even that of sunshine Injury of the nail readily provokes in the presence of this degeneration purpuric streaks (Berlin BJD 58 274 1946)

The disease is essentially asymptomatic and little can be done about it.

Necrobiosis Lipoidica, occurring not exclusively in patients with diabetes mellitus is characterized by asymptomatic plaques usually located on the lower extremities. Well-developed lesions are generally oval plaques, with well-defined borders and a smooth waxy surface. The central portions of the





Fig 335 —Cutis rhomboidalis nucha (Dr O G Costa.)

Fig 336 —Cutis rhomboidalis nuchae, H & E stain dermal papilla are flat, and degeneration of subpapillary tissue is apparent. (Dr Stuart C. Way)

lesions may appear somewhat sunken and atrophic or they may be xanthic and telangiectatic becoming coppery and of cartilaginous texture The outer zone is frequently violet (Hitch ADS 36 536 1937) The surrounding skin is normal. The common location is on the lower extremities, especially in the region of the ankle The onset is insidious and the chronic course is asymptomatic throughout unless ulceration occurs. Warty lesions and horny plugs have been known to develop on occasional lesions (Nousitou abs YBD 1943, p 190) and unlined cysts have been observed within the necrobiotic tissues (Sprafke DWehn 112 185 1941)

The condition appears histologically to be the analogue of mild, abortive superficial diabetic gangrene (Michelson and Laymon ADS 35 1130 1937) In their 6 patients trauma appeared to instigate the lesions. They (J 103 163 1934) noted the close alliance of these conditions. Changes occur primarily in the dermis where diffuse but patchy infiltration is seen with fibrotic and lymphocytic elements. Elongate and horizontally disposed necrobiotic masses of collagen appear pale and homogenized and Sudan staining reveals diffuse fat within these and droplets about them. Elastic fibers are absent within the areas and are sparse clumped, and fragmented in the vicinity Vessel walls are thickened, and there is proliferation of the intima with occasional thrombosis.

While similarity to granuloma annulare exists, the 2 diseases can be distinguished histologically (Ellis and Kirby-Smith ADS 45: 40, 1942 Laymon and Fisher ADS 59 150 1949) Xanthoma cells were demonstrable in a band surrounding the necrobiotic zone in the case of Nicholas (ADS 48 606 1943) Blood lipids are elevated (Rattner IllMJ 75 359 1939) A patient with hepatic and vascular disease but without diabetes was reported by Belote and Welton (ADS 40 887 1939) Diabetes was absent in 7 of 51 cases of Boldt (AfDuS 179 74 1939) and in 8 of 78 cases, among which 80% were females, reviewed by Hildebrand et al. (AIntM 66 851 1940)



Fig 337—Necrobiosis lipoidica in a diabetic.





Fig 338.—Necrobiosis lipoidica, affecting the shins. (Keisler and Caro ADS 30 796, 1934)

Fig. 339—Necrobiosis lipoidica diabeticorum note the homogenization and loss of nuclei in the connective tissue, with scattered round-cell infiltration. (Drs. Henry L. Michelson, and Carl W Laymon.)

No satisfactory therapy had been determined prior to the report of Burgess and Pritchard (ADS 57: 605 1948) that vitamin E, 250 mg per day appeared curative, but confirmation of their experience has been scanty Thyroid helped the patient of Bernstein (ADS 47 602, 1943) Excision and grafting were successful in a severe case exhibited by Cawley and Dingman (ADS 63: 764 1951) In a patient of Savitt (AD 71: 506 1955) good response followed intracutaneous injections of a suspension of hydrocortisone acetate

Nonspecific treatment includes local cleanliness, the careful avoidance of trauma and prolonged observation spontaneous improvement may be expected in the course of years spent at palliation. Diabetes should if present, be carefully controlled

Lipid Proteinosis (Lipidosis Cutis et Mucosae)—Urbach applied these titles to a rare familial and congenital disease clinically manifested by infiltrations into the skin and mucous membranes consisting mainly of lipid deposits. Hoarseness results from the pharyngeal and laryngeal involvement and is usually observed in early infancy According to Montgomery and Havens (AOtol 29 650 1939) cutaneous lesions may not appear until much later There is usually a pocklike eruption on the face appearing in infancy and leaving soft depressed scars. Extensor aspects of elbows, knees and







Fig. 890—Diffuse xanthoma lipidosis cutis et mucosae. (Wise and Rein: ADS 37 201 1938.)

Fig 891A—Diffuse xanthoma, Sudan III stain of frozen section note lipoidal mantling of vessels and absence of giant cells (Montgomery and Havens.)

Fig. 891B—Diffuse xanthoma, H and E stain of paraffin section note homogenization of collagen and perivascular clear spaces whence lipid has dissolved. (Montgomery and Havens AOtol 29 650, 1939.)

fingers are frequently involved, and the scalp may show only a sparse growth of hair The mucocutaneous junctions are affected as are the labial, lingual buccal pharyngeal and laryngeal mucosae There may develop the necessity for laryngotomy to prevent asphyxia. Some patients show indications of diabetes, and, while roentgen therapy is of no use, diet and insulin have seemed occasionally helpful

Microscopic examination reveals lipid sheaths about the blood vessels of the skin and mucosae, and massive lipid deposits in the cutis in the nodular type or keratotic formations in the hyperkeratotic type. There are no foam cells. The lipids are acetone-soluble phosphatides. A protein lipid combination is found in the deposits. The hyaline collections in the dermis contain a reduced lipid content electrophoresis shows increase in the alpha and beta globulins, and urinary excretion of amino acids, especially tyrosine, is increased (Braun and Weybrecht AfDuS 194 548 1952)

See Urbach and Wiethe (ArpathAnat 273, 285, 1929); Tripp (NYSJM 36: 619, 1936) first U.S. case; Wise and Rein (ADS 37: 201, 1938); Bazex (BaccFrancD 46: 136, 1939) case and review; Sandorny (Dermatologica 83: 375 1941) case; Will and Snow (ADS 43: 134 1941) liver damage and amyloid also present; Sulzberger (Laryng 52: 286, 1942) 29th case; Ramos e Silva (ADS 47: 301 1943) bullous and pustular lesions, histochemical studies showing protein phospholipid hyaline in superficial dermis; Price et al. (ADS 55: 42, 1947); Stenhouse (ADS 50: 56, 1944), improvement on lipocaic (?); Campbell (USNMB 42: 689 1944) improvement on insulin (?); Rothman and Fisher (ADS 55: 127 1947); Landt (ArDuS 188: 128, 1949), nonfamilial case with occasional hemorrhagic blebs, stomach involved; Holtz and Schulze (ArDuS 192: 206, 1951) 2 cases, recessive inheritance.

Xanthoma Disseminatum is described by Frank and Weidman (ADS 65: 88 1952) as a rare entity representative of systemic disorder involving the reticulo-endothelial system, particularly the reticulum cells and the histiocytes, differing from xanthoma tuberosum in that (1) cholesteremia is normal or low as shown by Thannhauser and Magendantz (AnnIntM 11: 1662, 1938) and (2) lesions are more commonly found on flexural skin areas. Lesions of mucous membranes, bones, liver, spleen, other viscera and the central nervous system tissues have been demonstrated. Nodules may originate in every organ where reticulum cells and histiocytes are normally present. The case reported by Frank and Weidman affected an old woman, whose illness began with a "cold" and fever following which she lost weight and noted the appearance of skin lesions about the neck, later on the lower abdomen and groins. Pinkish yellow sclerotic plaques were studded with numerous small yellow nodules. Some of these underwent ulceration and pain was severe not only in ulcers but also in deep infiltrative nonulcerated lesions. Blood cholesterol was normal. Blood pressure was 180/90. The patient was anemic and hypoproteinemic. Autopsy showed diffuse xanthoma affecting the skin and deep tissues, lymph nodes and some internal organs, as well as arteriosclerosis and tuberculous scars in the lungs and mesenteric nodes.

If the deposits in diffuse xanthoma underwent calcification a picture closely resembling calcinosis universalis (q v) would result.

Xanthoma and Visceral Disease.—Throughout the preceding descriptions, note has been taken of the systemic aspects and influences of lipid disease. Cutaneous xanthomas are occasionally associated with hepatic disease, especially with obstructive jaundice due to stricture of the common duct, whether inflammatory or neoplastic (Montgomery: JID 1: 325 1938) and in such cases the cutaneous xanthomas are usually secondary to the hepatic disease. The xanthomatous lesions appear light yellow in contrast with jaundiced skin. Despite marked hepatic damage as evidenced by clinical observations and liver function tests the normal ratio between cholesterol and cholesterol esters frequently remains undisturbed. There may be neither relative nor absolute increase in free cholesterol but relative or absolute increase in phosphatides (lecithin) is likely to occur and there is hyperlipemia. Palmar lesions are present in practically all cases of hepatic disease associated with cutaneous xanthoma. Disturbances in melanin pigmentation of the skin may also be encountered. I have seen this respond promptly to thyroid extract. Hyperlipemia, carotinemia, xanthosis, or xanthochromia and increase in the concentration of bilirubin in the serum do not necessarily parallel one another or correspond. Cutaneous xanthomas associated with hepatic disease may undergo involution as the condition of the liver apparently improves. Eruptions of red, circumscribed nodules which crusted centrally in 48 hours and healed with scarring and pigmented areolas were reported in a case of cirrhosis by Truffi (Dermatologica 80: 257 1939).

Occlusive arterial disease of the legs may be associated with tuberous xanthoma (Barker: AnnIntM 12: 1891 1939).

Xanthoma is recognized as a cause of sudden death because of its relation to coronary disease.

This was stressed by Muller (ActaMScand 1938, suppl. 89) and he (abs J 113: 662, 1939) reported 17 families in which there occurred by dominant inheritance heart disease associated with xanthoma. He thought that xanthomatosis causes a special kind of arteriosclerosis distinguishable from the usual form. Hypercholesteremia is present but hypertension is infrequent. A family of 9 brothers and sisters of whom 5 were xanthomatous and 4 died suddenly between the ages of 6 and 23 years, was recorded by Bloom et al. (ADS 45: 1, 194_). Young men with coronary disease, xanthoma and hypercholesteremia were studied by Engelberg and Newman (J 123: 1167 1943); see Cook et al. (AmJDisChild 73: 326, 1947) and Bigden and Willeford (J 14_: 120_ 1950) on sudden death in xanthomatous children.

In primary hypercholesteremic xanthomatosis, the plasma is clear while in idiopathic hyperlipemia it is milky. Clinical manifestations are similar, for tuberous and tendon xanthomas may occur in either. The study by Lever et al. (JID 22: 33 1954) of 7 cases of idiopathic hyperlipemia and 10 of hypercholesteremic xanthomatosis showed that

xanthelasma occurred only in the latter while in the former were observed papular xanthomas hepatosplenomegaly and abdominal cramps probably due to pancreatitis. Xanthomas of the Achilles, patellar and olecranon tendon rare in idiopathic hyperlipemia, were common in the other disease Xa thomas of th xtensor tendons of the fingers, tuberous xanthomas and coronary disease occurred frequently in both. While values for cholesterol and phospholipids were increased in both diseases, neutral fat were increased only in idiopathic hyperlipemia. Heparin injectio given for variou period of time to 5 pa tients of Lever et al. (AD 71: 150 158 1955) resulted in con iderable decreases in the turbidity and lipid values of the serums. Heparin locall injected into the lesions of 8 patients with tuberous xanthoma induced their flattening and disappearance observed Cornbleet (AD 71 17 1955)

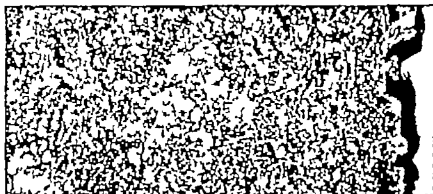


Fig 89.—X thoma t berosum fon cell are the large les ones (Dr Fred W hlman)

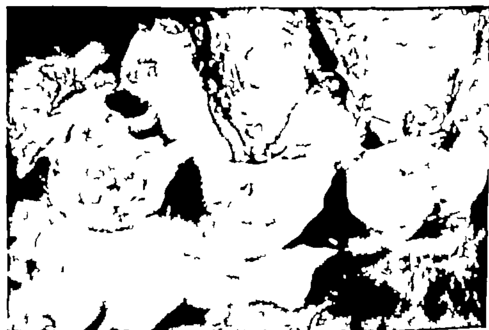


Fig 891 —Xanthomatous in lvement of th aortic alves resulting i ortic stenosis in a patient w th hypercholesteremic xanthomatosis (Barr J 156 942, 1954)

Erupt e x thoma occurring in the gl cogen storage disease of Von Gi rke (Beitr PathAnat 8° 407 1929) was discussed by Zakon et al (ADS 67: 146, 1953) as it was mani fested in a female inf nt who came to autopsy. The skin was st dded with discrete firm yellow papules and nod les numerou especially on the neck, scalp a d elbows, and also present on the k ees soles and buttocks. The live edge rea hed the umbilicus and the belly was distended. There was no lympha lenopathy

Eruptive xanthoma with both pl and t berose lesions ccompanied marked enlarge me t of spleen and live hro I jaundice and normously in reased blood le ls of cholesterol, total phospholipid d neutral fat in a boy with congenital acholangic biliary cirrhosis studied by Ma Mahon a l Thannhauser (Ga troenterol 1 455, 1952)

Hyperlipemic xanthomatosis occurred in a patient with subacute glomerulonephritis, eruptive xanthoma being secondary to the nephrotic stage of the nephritis with its hyperlipemia, reported Taylor and Curtis (ADS 70: 618 1954)

Etiology Pathology and Treatment of Xanthoma.—The causes of lipid disturbances are incompletely known Xanthoma tuberosum perhaps represents irritative connective tissue hyperplasia due to extravasated lipid. The presence of lipids in the cells does not appear to affect their vitality but makes them foamy in appearance. Probably any cell capable of phagocytism is capable of becoming a xanthoma cell which is a reticulo-endothelial cell modified by the storage of cholesterol esters (Plewes ArchPath 17 177 1934) Giant cells are common During regression such cells may come to resemble those of spindle-cell sarcoma (Weldman and Schaffer ADS 35 767 1937) Lesions have been produced in the skins of rabbits by feeding the animals cholesterol (Rusch et al ArchPath 28: 163 1939)

While diet helps in hyperlipemic xanthomatosis, the production of xanthoma in normal persons does not result from limiting them to a ketogenic diet (carbohydrate 25 gm fat 200 gm., protein 60 gm.) It seems that the reticular cells may either make or store cholesterol and in xanthoma they are unable to get rid of it a biochemical defect which is often heritable Despite a diet free of cholesterol and pursued for 13 years, the patient of Schick and Sperry (AmJDisChild 77 164 1949) continued to exhibit hypercholesteremia and unresponsive xanthomas although he did not develop new lesions. Thyroid insulin and other therapeutic endeavors did no good This patient like many was one of a family in which hypercholesteremia was inherited.

Hypercholesteremia is heritable with or without xanthoma stated Fliegelman et al. (ADS 58 409 1948) in a genetic study of a large family In some families hypercholesteremia is inherited as a dominant (Miller and Rogers Sci 109 61 1949) resulting in angina coronary artery disease familial xanthelasma and xanthoma Genetic studies of atherosclerosis in relation to familial xanthoma were pursued by Adlersberg et al. (J 141: 246 1949)

Electrophoretic analyses of the serums of patients with primary familial xanthomatosis and with biliary cirrhosis showed marked increase in the size of the beta 1 peak (Lever and MacLean JID 15 173 1950) Serum lipoproteins and cholesterol metabolism were studied in 35 cases of xanthelasma among whom 17 were hypercholesteremic and 7 suffered from advanced coronary disease (Epstein et al. ADS 65: 70 1952) The presence of xanthelasma is indication for careful investigation of the cardiovascular system. Instructive articles are those of Montgomery and Osterberg (ADS 37 373 1938) and Wilder (AIntM 61: 297 1938) Unusually extensive atherosclerosis involved the aorta its main branches, the endocardium and several valves of the heart in the young man with familial hypercholesteremic xanthomatosis studied by Barr et al. (J 156 943 1954)

To encourage elimination of lipid deposits, restriction of animal fat in the diet medication with thyroxin, perhaps iodides, even garlic, and in non lipemic deposits, x radiation may be useful therapeutic measures. When xanthomatous tissue forms despite the existence of a practically normal level of lipemia, as it does in the disseminated forms in contrast with the eruptive forms little benefit may be expected. Cardiac damage eruptive xanthoma, and low BMR were the features of a patient much benefited by low fat diet and thyroxin (Delp JKansMS 41 95 1940) Vitamin A, 200 000 units, and 0.5 Gm dehydrocholic acid daily yielded an excellent result for Montgomery (ADS 51 214 1945) in 1 patient.

Control of the atherosclerotic process may be approached by (1) restriction of caloric and lipid intake substituting vegetable fat for animal (2) stimulation of oxidative processes by giving a diet rich in proteins, oxytropic members of the vitamin B complex, including nicotinic acid, thiamine and riboflavin, and small amounts of thyroid hormone (3) decholesterolization of tissue depots by giving lipotropic factors of the vitamin B complex, choline inositol and piridoxine and (4) stabilizing the plasma cholesterol with adequate amounts of colloidal stabilizers, such as lecithin and albumin (Hueper MPath 38 162 243 350 1944 39 51 117 187 1945)

Lipocaic, a pancreatic extract which permits survival and prevents liver changes in depancreatized dogs (Dragstedt et al.: AIntM 64: 1017 193) has been tried in xanthoma tuberosum by Rosenak (AnnIntM 10: 511 1943) but it failed to alter the serum cholesterol or the cutaneous lesions. See Dragstedt (J 114: 70, 1940)

Sitosterol given by mouth reduce th intestinal absorption of cholesterol and so hold down cholesteremia according to Pollack (Circulation 7: 702, 1953)

Pressure bandages used continuously over a long period of time may reduce the size of xanthomatous nodules (Butterworth: AIH 69 545, 1953)

CAROTENEMIA

Carotenoid pigmentation is the dermatologic manifestation of this metabolic error The region of the nasolabial folds and the palms and soles are the sites of predilection affected in mild cases when severe pigmentation is generalized excepting the sclerae (Heymann J 106 2050 1936) Carotenoid pigments color the blood serum account for 10 to 50% of the color of plasma and fix themselves in the fat of the dermis and subcutaneous tissue and in the keratin of the epidermis and sebaceous glands (Jeghers NEngJM 228 678, 1943) Cutaneous changes generally result from overingestion of lipochromes, which are richly present in orange carrot egg yolk, and other brightly colored foods (Rattner and Ginsberg ADS 40 831 1939 Rosen ib 44: 750 1941)

Aurantiasis was the name given the disorder when it results merely from overingestion (Hashimoto: J 9 1111 1922) Cases occurring in persons following eccentric diet were noted recently by Wolf (ADS 61: 131 1950) Aukland (BMJ 2: 907 1932) and McConaghey (Lancet : 714 195)

Carotene is closely allied to vitamin A for hydrolysis of the double bond between the symmetric halves of the carotene molecule result in the formation of two molecules of vitamin A a conversion normally accomplished by the liver (Ralli et al.: JLabClinM 20: 1266 1935; Stueck et al.: J 109: 343, 193) after it absorption from the intestine (Heymann AmJDisChild 51: 273 1936)

Carotenoid pigmentation is seen as a result of abnormal metabolism rather than of abnormal dieting in diabetes, xanthoma and myxedema (Boeck and Yater JLabClinM 14 1129 1929 Almond and Logan BMJ 2 239 1942; Escamilla JClinEndocrin 2 33 1942)

In poliomyelitis, only a rare case did not show some degree of xanthosis cutis in the acute phase of the disease reported Linn (MJAustral 1 581 1954) in whose patients serum lipochrome indices were not much abnormal serum carotine levels were usually normal, yet yellow-green fluorescence of the palms was seen when they were exposed to filtered UV light The same findings were observed in patients with encephalitis complicating acute infections, but not in other patients.

In distinguishing carotenoid pigmentation from jaundice Caviness (N CarolMJ 5 432, 1944) noted that in carotenemia pruritus does not occur the sclerae are clear the urine is less dark and does not contain bile the blood bilirubin is not increased and the stools are normal A test devised by Greene and Blackford (MedClinNoAm 10 733 1926) consists in overlaying the serum protein in a test tube with alcohol which dissolves the bilirubin, and then with petroleum ether which takes up the lipochromes.

In treatment the diet should be altered to exclude yellow substances, the underlying metabolic defect sought out and corrected if possible and thyroid given if indicated

URTICARIA PIGMENTOSA

Urticaria pigmentosa (xanthelasmoidea) is characterized by the occurrence of yellowish or brownish pigmented lesions which manifest urticarial irritability when mechanically stimulated. The disorder is comparatively rare Since the original description by Nettleship (BMJ 2 324 1869) and the reviews by Blumer (MonatshprakD 34 213 1902) and Graham Little (BJD 17 355 393 427 1905 18 16 1906) Finnerud (ADS 8 344 1923) was able to find records of 152 additional cases.

The disease generally begins in early infancy with the appearance of wheals, papules and nodules which may not at first be differentiated from

those occurring in urticaria of the ordinary type Cases fall clinically into the 3 varieties macular nodular and mixed The nodular type is suggestively similar to xanthoma Scarring on involution is rare but is associated especially with the nodular lesions. Lesions may be present at birth (Boardman ADS 43 570 1941) resembling nevoxanthoendothelioma (q v) Bulla formation sometimes occurs Finnerud having listed 8 cases see Tavs (ADS 55 558, 1947) Bullous lesions were present at birth in an extensive nodular case





Fig. 894.—Urticaria pigmentosa. Several lesions became vesicular (Drs. A. P Biddle and R. A. C. Wollenberg.)

Fig. 895.—Urticaria pigmentosa. (Dr L. W Ketron.)

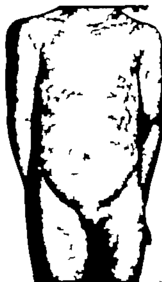




Fig. 896 —Macular urticaria pigmentosa.

Fig. 897 —Nodular urticaria pigmentosa in boy 7 months old.

reported by Lipschutz and Shaffer (JI ed 39 745 1951) Lesions were papular and vesicular in 1 infant and bullous only in another reported by Dewar and Milne (AD 71 717 1955)

Dermographism is limited to the lesions and does not affect the intervening normal skin this phenomenon is called Darier's sign. Darier's sign is not necessarily uniformly positive; in some cases urtication follows rubbing only at certain times (Engman quoted by Reiches ADS 70 377 1954) Itching may be severe The trunk seldom escapes involvement but no region is exempt Lymph node enlargement is commonly present There is no interference with health and well being The lesions are variable in number sometimes being few or even solitary The case of Gross (ADS 29 451 764 1934) was a solitary mast cell tumor 2 cm in diameter on the thigh of a boy 5 months old 10 cases with solitary lesions were reported as occurring generally in infants 3 months old or younger by Chargin and Sachs (ADS 69 345 1954) Urticaria pigmentosa has been observed in uniovular twins in at least 4 instances (Trejeiro and Bonafina abs BJD 66 265 1954)

The onset may occur after puberty (Adamson BJD 35 222, 1923) According to Hannay (BJD 37 1 1925) the adult and juvenile types are not distinct but are intergradient Cases in adults characteristically present mild urticarial symptoms the lesions being small, macular or almost macular and often telangiectatic (Barber and Weber InternatClin 4 71 1932)

INCIDENCE BY AGE OF ONSET IN 286 CASES OF URTICARIA PIGMENTOSA (HANNAY 1923)

AGE	CASES	AGE	CASES
1 5	194	30-35	6
5 10	14	35 40	9
10 15	16	40-45	6
15-20	13	45-50	3
20 25	11	After 50	5
25-30	11		

In a statistical study of 300 cases (Flanerud 1923) 53.3% of the patients were males, and 46.7% were females Of 143 cases in which the age at onset was given, 46.1% began within the first year 67.1% before the thirteenth year and 32.9% were adult cases. Of the 141 cases in which the type of lesion could be determined 61 % were macular 7.5% nodular and 30.5% maculonodular

Some of the lesions disappear spontaneously but the majority persist and in the course of a week *or so a new lesion becomes more or less pigmented*. When in close proximity the wheals sometimes coalesce but seldom form large patches like those so frequently seen in acute urticaria Individual wheals and nodules are slightly elevated, with firm and well-defined bases and a chamois or brownish color New lesions develop from time to time and the older ones gradually subside *sometimes leaving atrophic* spots, or even cicatrices The evolution of the disease *en poussées* has been remarked by many including Török (HandbHuG 6 2 216 1928) Itching may be slight or entirely lacking but it is usually severe from the beginning Itching and pigmentation may persist long after the disappearance of the lesions. The duration of the disease is indefinite Comparatively quiescent periods are noted as a rule for periods of weeks or even months.

Urticaria pigmentosa, originally described as a purely cutaneous condition has been recognized only relatively recently as being systemic. Ellis (APath 48 426 1949) found at autopsy of a 1 year-old child hepatomegaly splenomegaly and extensive mast cell proliferation in the liver spleen bone marrow lymph nodes, kidneys and perirenal fat Mast cell disease is a common tumor of dogs, in which occur widespread reticuloendothelial lesions. The human patient of Reilly et al (AD 71 581 1955) presented infiltrations in the skin, liver and bone marrow Systemic involvement of an old man studied by Berlin (AD 71 703 1955) was manifested by a cutaneous hemorrhagic tendency severe and progressive anemia with leukopenia and thrombopenia, enlargement of the liver and spleen and the presence of mast cells in considerable numbers

in the bone marrow The eruption in this patient was widespread, papular and nodular and both discrete and confluent and it was present in the mucosa of the nasal cavity and oropharynx.

There is a type of pigmentary urticaria in which the lesions clinically resemble those of the usual form but when examined histologically are found to be entirely free of the characteristic mast cells. Ormsby (JCutDis 35: 850 1917) exhibited such a case and Sutton (JCutDis 35 749 1917) reported a second one. Both patients were young women, and the lesions had developed quickly and after puberty

Nonpigmented persistent papules with Darier's sign and mastocytosis were reported by Sézary et al. (BSocFrançD 43 78, 1936) The absence of itching was the unusual feature of one case (ADS 34: 304, 1936) The eruption was generalized and composed of confluent small yellowish elements in the remarkable case affecting a young woman reported by Graham et al. (ADS 45: 906 1942) histologically the lesions were packed with mast cells. Some of the lesions were verrucous in the unusual adult female patient of Goldsmith and Wells (BJD 64 200 1952)

Etiology and Pathology—Little is settled regarding the etiology The majority of the cases occur in infants. The disturbance appears to be a metabolic one for the patients seem to be in perfect health except for their pigmentary urticaria like most patients with xanthoma. Histologically the lesions resemble those of ordinary urticaria, but instead of the usual collection of leukocytes there is usually but not always, an infiltration of mast cells.

Splenomegaly and myeloid blood changes have been noted in some cases (Touraine et al.: BSocFrançD 40: 1691, 1933; 41: 1911, 1934) The systemic nature of the disease was evidenced by the findings in a female infant who died of pulmonary edema, reported by Elli (ArchPath 48: 426 1949) This unique necropsy disclosed mast cell infiltrations of mesenteric lymph nodes, spleen liver and bone marrow as well as the cutaneous tumors.

Various osseous lesions have been noted in a few cases by Clyman and Rein (JID 19: 179 1952) the significance being as yet unknown. Small defects in the skull were discovered also by Calnan (BJD 65: 375, 1953) in 2 cases so that one may give thought to the French classification of the disease as related to that of Hand-Schüller-Christian, a mast-cell reticulosis (Hissard et al.: PresseMéd 63: 1765 1951) Osteoporosis of lumbar vertebrae and pelvic bones was unexplained in a young man with telangiectatic urticaria pigmentosa seen by Bluefarb and Salk (ADS 70: 3 6, 1954)

The metachromatism of mast cells is due to heparin (Holmgren and Wilander: ZtschrMikroskAnat 42: 242 1937) or to a sulfuric mucopolysaccharide related to heparin and to hyaluronic acid (Asboe-Hansen: CancRes 13: 587 1953) Tissue mast cells contain histamine (Riley: Sci 118: 332, 1953) The relation of these observations to urticaria pigmentosa is unknown. Urticaria pigmentosa with a glomus tumor lesion was seen in a woman of 53 by Pautrier (BullSocFrançD 46: 511 1939) The case affecting an infant reported by Moynahan (BJD 61: 425 1949) showed many mast cells, which may be a common denominator with telangiectasia macularis eruptiva perstans (q.v.) the differential diagnosis of which was described in detail by Mourmand and Hirschmann (ADS 63 242, 1951)

Mast cells were grown in tissue culture from a lesion of urticaria pigmentosa by Zitcer and Kirk (Sci 119 99 1954)

Involvement of uniovular male twin infants was observed by Tejeiro and Bonafin (abs YBD 1954 p 242)

Treatment.—No therapeutic effort is known to be dependable. Dramatic response to ACTH in one case was claimed by Robbins (ADS 70: 232, 1954) Whealing was prevented by the oral administration of Benadryl in the case of Saunders and Miller (JID 11 309 1948)

The disease usually tends to disappear as puberty is reached. In one patient first exhibited at age 16 the condition persisted for at least 40 years (Touraine BSocFrançD 46 52, 1939) Pigmentation in adult cases is generally persistent While urticaria pigmentosa can be astonishing in appearance, it seldom causes consequential distress and may be considered basically innocuous in the usual case

The metachromatic material of mast cells apparently is heparin (Holmgren and Wilander ZtschrMikrAnat 42 242, 1937) and the relation of heparin with urticaria pigmentosa was discussed by Kierland and Stegmaier (ADS 62 28 1950) without reaching conclusions. Since heparin is altered



Fig 598.—Urticaria pigmentosa in adult (Dr D F H Cleveland)

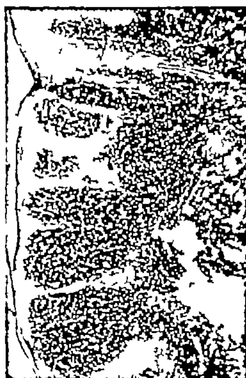




Fig. 599 —Urticaria pigmentosa dense mast cell infiltration
Fig 600 —Urticaria pigmentosa, showing vesicle formation. Dr William Allen Pusey)

by toluidine blue an antiheparin agent an adult male patient was given the dye in a dose of 300 mg daily by mouth and was relieved of urtication for the most part while taking it reported Lorincz (ADS 65 745 1952) The dye failed to relieve the patient of Drennan and Beare (BJD 63 257 1951) a case not controlled by antihistamine drugs either Concerning toluidine blue see Thrombocytopenic purpura treatment (p 757) A trial of injections of protamine sulfate would be interesting

Because desoxycorticosterone induces the disappearance of mast cells from canine mast cell tumors and reduces the heparin level in hyperheparinemia Urbach et al. (ADS 70 675 1954) administered 4 mg daily by sublingual absorption to a woman with extensive involvement and claimed striking benefit. Urbach stated that cortisone may release heparin so rapidly that acute bleeding phenomena may occur in dogs with mast cell tumors.

Bulla formation followed intradermal injection of heparin into either a papule or the normal skin of a patient of Konrad and Winkler (Hautarzt 4: 119 1953) Heparin could not be found in biopsy tissue examined by Cornbleet (ADS 70 347 1954)

TELANGIECTASIA MACULARIS ERUPTIVA PERSTANS

Under this title Barber and Weber (InternatClin 4 71 1932) collated cases manifesting telangiectases appearing over the chest abdomen and thighs, and showing an interesting interrelationship with urticaria pigmentosa. The eruption consists of discrete small elements which become persistent telangiectases manifesting a brown stain on diascopy One may surmise that toxic metabolic substances may damage blood vessel walls, as one observes when spider nevi follow overingestion of butterfat chocolate or cod-liver oil and regress after a few months when the diet is altered.

Barber and Weber reviewed Vidal's case (Colcott Fox's *essential tela giectasis i plaques* BJD 20: 145, 1908) a woman who suffered from urticaria at the onset of menstruation soon after which permanent red macules began to appea ; and Osler's case (*t la giectasis ci cumscripta universalis*, BullJHH 18: 401 1907) a man f 39 years whose dark red, lenticular and confluent eruption involved large portions f the trunk and extremities, and on whom factitious urticaria could readily be produced and Webe and Hellenschmied case (*t la giectasia macularis eruptiva perstans*, BJD 42 374, 1930), an obese woman of 60 years, whose generalized, m cular telangiectasi showed brownish pigmentation upon diascopic pressure and was presented as a tela giectatic variety of urticaria pigmentosa in an adult ; nd the case f Weber (ProcRoySocM 25: 665 1932) of urticaria pigmentosa in an bese woman of 30 years, whose eruption consisted of brownish red macules th t t ded to become confluent on the legs and the case of Barber (ProcRoySocM 25: 1029 1932) a bese woman of 56 years, whose eruptio over the breasts, bdomen, thighs and popliteal spaces, was dull red, telangiectatic and m cular but on the i aspects of the upper extremities wa sym metric, paler less telangiectatic and definitely of the urticaria pigmentosa type, and became urt carial and pruriginou on friction. Such cases h ve been described a *telangiectasies acquises généralisées* by Lévi, and as *telangiectasies essentielles en plaques acquisés* by Brocq.

In a case reported by Keisler and Becker (ADS 33 109 1936) the lesions were histologically benign melanomas when fully developed and stationary; this woman had urticaria for years. The patient of Kra tz (DWebn 102: 377 1936) a woman of 43 ears, said h red-brow macules had been comi g on for 1 ears. The 10- ear-old patient f Ball (ADS 36: 65 1937) i represent tive of the intermingling of characters of both urticaria pigmentosa (q v) and telangiecta ia. Generalized a giomatosi appeared f llowing the admin istration of 1 yrille rami e t a man with an urticarial eruption reported by Oppenheim nd Yaculio (BJD 60: 369, 1948)

SEBORRHEA

Seborrhea is a functional disorder manifested by an increase in the amount of the sebaceous secretions. Under normal conditions sebum (q v) consists of various lipids, dry epithelial cells, and epithelial cells undergoing fatty degenerative changes. A certain amount of this material is constantly being supplied serving to protect the integument Seborrhea may consist in excessive production of either fatty substances or dry epidermic cells. The

excess production of oil characteristically gives the skin a shiny greasy appearance See Physiology sebaceous glands, also Butcher and Parnell (JID 9 67 1947)

Seborrhea Sicca is the form characterized by the accumulation of scales or crusts in addition to the abnormal oiliness. This manifestation is doubtless due to infection or malnutrition of the epidermis (see seborrheic dermatitis)

Seborrhea Oleosa.—This occurs most frequently during the period of adolescence While the face particularly the nose and forehead, and the scalp are conspicuous sites for the disease other regions are simultaneously involved. This kind of greasiness of the skin, unaccompanied by comedo formation and acne is not responsive to low fat diet and the patients, often red haired, do not tolerate medication with thyroxin.

That the diet is related to the oiliness of the skin is indubitable. I think I am able to recognize at a glance persons who consume large quantities of milk (a glandular product possibly having hormonal effects) judging simply by the large pores, oily skin greasy rugose thickened telangiectatic nose the many comedones milia and superficially located sebaceous cysts and the scattered hypertrophic sebaceous glands.

While seborrhea oleosa may be caused by dietary excess of oil beyond the ability of the metabolic processes to dispose of it the cause may lie in the inadequacy of the metabolic processes rather than in their being overloaded. Hyperlipemia is a characteristic feature of hypothyroidism and hyperlipemia results from the ingestion of iodides. Thyroid extract diminishes hyperlipemia much as insulin diminishes hyperglycemia Hypothyroidism is a common cause of seborrhea. It may also be caused by trypanosomiasis (q v) Seborrhea is often one sequel of epidemic encephalitis and accompanies Parkinson's disease (Cornbleet et al ADS 54 93 1946 Elliott BMJ 2 861 1948 Kvorning ActaD-V 32 201 1952) There are numerous cases of seborrhea which do not respond to low fat diet with coincidental administration of thyroid extract in my experience these are the cases which in men are associated particularly with premature alopecia and in women, with a type of acne vulgaris that is particularly unresponsive to treatment

There are more etiologic factors involved than are understood at present That they are concerned with chemical processes and hormone or vitamin function I do not doubt The antagonistic relationship of vitamin A with thyroxin is interesting in this connection I have seen cod liver oil cause seborrhea and acne vulgaris. It has been said that reflex congestion of the skin from any cause is a factor predisposing to seborrhea and that indigestion, constipation and similar disorders are often contributory if not causative of it. These may sometimes be symptoms of hypothyroidism.

The skin of the seborrheic subject is apt to be a veritable hotbed for the growth of *Pityrosporum Corynebacterium acnes* and *Staphylococcus albus*, Barber (Pract 14 : 1 1939) pointed out. He attributed aggravation of the seborrheic state" not only to excess of fat but also to *concentrated carbohydrate foods and to alcohol*. His review of the relationship of the diet with dermatoses is instructive and provocative of thought. M rehfoolal et al. (AfDuS 176 613 1939) presented an extensive study of the biochemistry of the skin in seborrhea.

That the seborrheic tendency is inherited, as are likewise the tendency to keloid, xanthoma, acne vulgaris and premature baldness, must be admitted. While Cockayne (Inherited Abnormalities of the Skin Oxford University Press, 1933) did not know of complete pedigrees showing the inheritance of seborrhea, he quoted Jacquet's account of a family of 13 persons, 12 of whom were to a high degree seborrheic and he also quoted Barber "There may be a hereditary and congenital predisposition to the seborrheic state. Seborrheic families are common enough and, conversely certain families appear to be almost immune." Barber (1939) was convinced that heredity is an important factor in so-called seborrheic alopecia, a view with which many agree. Seborrhea probably represents a particular pattern of chemical and metabolic make-up, just as xanthomatosis and the tendency to keloid formation do and it is similarly heritable. The investigation of uniovular twins by Siemens (AfDuS 160: 45 1930) indicated that heredity plays a large part in the etiology of seborrhea.

Sabouraud (Nouvelle Pratique Dermatologique Masson 1936) wrote "We are forced to abridge the chapter on pathogenesis of seborrhea: we know almost nothing about it. We see its appearance and its first development coincide with *the awakening of puberty* The development of sexuality is at the basis of the development of seborrhea; the mechanism which relates these two facts is unknown to us, as well as the role of the microbacillus."

Testosterone increases the size and function of sebaceous glands and stilbestrol diminishes these (Rony and Zakon: ADS 52: 323, 1945). Progesterone influences the sebaceous glands of the female in a manner similar to androgen.

Treatment.—Underlying constitutional factors, such as acromegaly, hypothyroidism, overingestion of fatty foods and the ill-advised overconsumption of vitamin concentrates, should if possible be remedied. Roentgen therapy, sulfur and resorcinol are the most valuable in those instances presenting involvement of the glabrous skin, and sulfur, resorcinol and mercury in the hairy regions. The skin should be cleansed frequently with soap and water, alcohol or benzene. Alderson (ADS 8: 414, 1923) advocated carbon tetrachloride, which was first employed in dermatology by Jacquement and Goubeau, and the value of which lies in its action as a fat solvent. Of the various sulfur preparations, lotio alba is one of the best. It may be applied at night and a powder consisting of sulfur 1 part, and talcum 8 parts, may be dusted freely over the surface during the day. Alcoholic solutions containing 1 to 10% resorcinol sometimes prove more satisfactory than sulfur. The treatment of the scalp is considered under the alopecias and under seborrheic dermatitis. *Estrogenic hormones sometimes diminish the oiliness of the skin in seborrhea oleosa,* but my results with their use for this purpose have been unsatisfactory.

ROSACEA

Symptoms.—Rosacea is a chronic disorder of the nose and face characterized by diffuse inflammation, telangiectasis, seborrhea and acneiform inflammatory lesions. It begins generally on the nose with redness and seborrheic hyperactivity. The process spreads to contiguous areas on the cheeks, involving sometimes the forehead and chin. Crops of acneiform lesions complicate the picture. These are not built about solid comedones, however. They are less acuminate than ordinary acne pustules, and their summits undergo pustulation so as to form comparatively shallow pockets. They may be deeply seated and painful but on resolution leave no scar. In severe cases, the skin is thickened, infiltrated and purplish, and the inflammation surrounding separate pustules is confluent.

Keratitis and conjunctivitis are sometimes associated with rosacea. Conjunctivitis may be severe, manifesting small papules of pinhead size surrounded by a ring of dilated capillaries (Low: BJD 34: 275, 1922). Blepharitis also occurs (Doggart: BMJ 2: 702, 1937). Iritis accompanying rosacea may occur without corneal involvement (Oláh: abs ADS 41: 578, 1940). Vascularization of the cornea may develop. The Negro seems immune to ocular manifestations (Wise: AmJOphth 26: 591, 1943). Eye changes occurred in only 1.2% of 565 cases reviewed by Mazzini (abs YBD 1943, p. 245). Achlorhydria is found in some patients with keratitis, according to Johnson and Eckhardt (AJOphth 23: 899, 1940), who obtained excellent therapeutic results in the eyes and erratic improvement of the skin with 3 to 5 mg. of riboflavin daily. Patients with keratitis reacted positively to testosterone on intradermal testing, but not to other hormones, and they could be desensitized, wrote Zondek et al (BritJOphth 31: 145, 1947), who surmised that these patients were allergic to endogenous glandular metabolites.

Studying 99 patients with both cutaneous and ocular lesions, Borrie (BJD 65: 458, 1953) found that ocular lesions were relatively more common in men, that the cutaneous lesion appeared first in 53% of cases and the ocular in 20%, and that each could precede the other by anything up to 30 years; and that, while keratitis was by far the commonest ocular manifestation, iritis did occur without preceding keratitis, and blepharitis alone was probably secondary to seborrhea and not to rosacea. He concluded that the cutaneous and ocular lesions of rosacea, though having the same basic cause, are otherwise independent of each other, and that the disease does not spread from the skin to the eye or vice versa.

Minor ocular troubles, such as blepharitis, conjunctivitis and marginal ulcers, are common in rosacea, stated Goldsmith (BJD 65: 448, 1953), but they are not specific to the disease and no inference should therefore be drawn as to its fundamental nature from

their clinical course and response to treatment. However severe keratitis is specific, and although once having developed it may progress quite independently of the skin lesions, one may assume that both have the same pathogenesis. The most effective form of treatment presently available for the severe ocular lesion seems to be x-ray therapy.

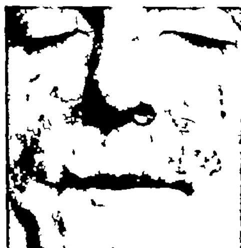



Fig. 901.—Rosacea. (Dr. Herbert Brown.)
Fig. 902.—Rosacea.




Fig. 903.—Rosacea.
Fig. 904.—Rosacea.

Etiology.—Rosacea is said to develop as a result of any disorder which gives rise to persistent reflex flushing of the face. The condition is commoner in women. Thyroid and gonadal disturbance, dyspepsia, constipation and overindulgence in alcohol, tea or coffee are associated. Seborrhea, acne and seborrheic dermatitis are frequently coincident affections. *Demodex folliculorum* may play some part in pustulation (Ayres and Anderson: ADS 25: 89,

1932 Brodie: AustralJD 1: 149 1952) Gastric subacidity was no more frequently detected in rosacea than in other dermatoses tested by Brown et al. (BJD 47 181 1935)

Rosacea seems to me to be a clinical designation analogous to pompholyx in that various causes may produce almost indistinguishable eruptions. The name is correctly applicable perhaps exclusively to a disorder of metabolism, presumably of lipids. I surmise that the fatty substances provocative of rosacea are liquid at body temperature in contrast with the comedo-forming relatively solid substances which constitute the comedones and incite the pustulation of acne vulgaris. Sebaceous folliculitis of infection can be *morphologically similar. Focal infection too is capable of causing rosacea* if the name is used in a clinical rather than an etiologic connotation. See Rosacea like folliculitis. Since some cases of rosacea are cured by eliminating certain foods from the diet the disease may in some instances represent allergy. Chocolate nuts and tomatoes I find now and then seemingly specifically offensive. Even when such ingesta are causative it is far from clear that allergy is the mechanism whereby they excite trouble.

Few cases resembling the rosacea like tuberculid are tuberculous. While tuberculoid structure of the inflammatory lesions of rosacea occurs in the minority of them the relation with tuberculosis is obscure, and tuberculoid structure is no proof of tuberculous etiology (Laymon and Schoch ADS 58 286 1948 Laymon ADS 63 409 1951) The rosacea like tuberculid is actually quite rare.

Some cases of rosacea perhaps those related to *Demodex* respond to 40% sulfur paste. Some are much benefited by estrogen in balanced dosage, others by low fat low-carotenoid diet still others by the administration of riboflavin pantothenic acid or other members of the B complex, along with hydrochloric acid. Elimination of foci is essential and Vioform ointment is helpful locally in yet other cases. To tell which variety of rosacea the patient has at the first visit is a problem which still baffles me. Gastroscopic studies by Usher (ADS 44 251 1941) revealed gastritis, the severity of which paralleled the severity of the rosacea but was not related to hydrochloric acid.

Studies of blood vessel physiology in patients with rosacea were made by Borrie (BJD 67 5 73 1955) who found no differences from controls in skin temperature readings under various conditions or in responses to injections of various physiologically active agents.

Treatment.—It is traditional to restrict alcohol, coffee tea, pork, sausage, foods rich in shortening highly seasoned or extremely hot or cold foods, cheese pastries and nuts. As the main therapeutic measure Bommer (YBD 1937 p 401) recommended regulation of the diet utilizing according to severity and tolerance, diets of (1) fruit, vegetable and carbohydrate with a minimum of fat and protein or (2) milk and cream additionally or (3) 300 gm. meat and 2 eggs a week in addition to this. External therapy he regarded as superfluous. Once clear the patient may try prohibited foods, and lesions reappear within 12 hours when an offending one is eaten. I often prescribe a low fat, low-carotenoid diet restricting milk, cream, butter ice cream chocolate, nuts, carrot, orange, sweet potato, tomato and egg yolk, especially. Female patients are usually constipated and often habituated to taking mineral oil from which they must be weaned with the help of a bulky diet and an increase in ingested fluids. Riboflavin is promptly effectual in ocular rosacea Cole told me confirming Johnson and Eckhardt (1940) although Wise (1943) did not believe rosacea to be a manifestation of ariboflavinosis. Dilute HCl should be given with meals, 1 0 cc with water t.i.d. if achlorhydria is present.

For external treatment reliance is placed mainly on sulfur and resorcinol lotions. I often prescribe with satisfaction Vioform Cream with 3% sulfur added to it. Telangiectases can be remedied with the electric needle. Refrigeration therapy has been recommended the CO_2-acetone slush being favored by Cohen (PostgradMJ 24 656 1948) Roentgen therapy is of little value. The combination of 2% salicylic acid and 5% ammoniated mercury in an ointment

is sometimes quite effective Staley showed me Systematic massage of the affected skin was recommended by Sobye (abs YBD 1951 p 70) a physiotherapeutic method I have not tried Treatment of concomitant seborrheic dermatitis of the scalp is advisable (Butler ADS 33 729 1936) since corneal lesions like those occurring in rosacea may be seen in seborrheic dermatitis (O Donovan and Michaelson Brit J Ophth 30 193 1946)

Elimination of focal infection is essential in the management of some cases (Feit et al J 105 1738 1935)

ACNE VULGARIS

Comedones (Blackheads) are masses of accumulated sebaceous matter blocking the ducts of oil glands, usually semisolid in consistency and capped at the follicular orifice with a layer of horny débris dark from oxidation. Occasionally the plugs are comparatively hard and can be expressed as firm,



Fig 905.—Ordinary comedonic and papular acne
Fig. 906—Comedo blocking hyperkeratotic sebaceous orifice no inflammation

oat grain-shaped semitranslucent bodies. The face is the commonest site of the lesions, although the concha, the upper dorsal skin of the trunk, the sternal region nucha axillae, groins and perianal skin, and the scrotum and shaft of the penis may be involved. Exceptionally the lesions may exhibit a tendency to symmetric grouping They can be expressed and emerge from the follicular orifices as greasy wormlike masses. There may be some associated inflammation. When inflammation is present it characteristically includes phagocytic leukocytes and foreign body giant cells denoting tissue reaction to comedo lipid This inflammatory reaction is acne vulgaris. Follicular coccic inflammation resembles foreign body reaction to comedo lipid, for both are furuncle-like in configuration but they differ in clinical course cause and histologic structure.

Comedones Occurring in Groups, small symmetricall on the temples and cheeks, are occasionally seen (Crocke Lancet 1 813, 1835 Thin Lancet 1 71, 1835 Wetherell and Sympson Lancet 1 169 1889 Doucas ADS 56 376 1947)

I have seen cases affecting the face in young children, where an oval region measuring about 1 by 3 cm. exhibited rosy erythema with margin which was not sharp and within which numerous, close-set tiny comedones and milia were grouped. These solitary lesions persisted for many months but yielded to x ray therapy I could not determine the cause.

Comedones commonly develop about the edges of irradiation scars on the face (Bl efarb: AD&S 56: 537 1947 Hartman: AD&S 62: 440 1950) especially after roentgen therapy of basal cell carcinoma.



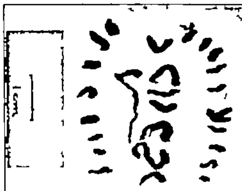


Fig 907—Ordinary pustular acne (Beerman: MedClinNoAm, p. 1160, July 1953)
Fig. 908.—Comedones. (Dr Fred Weidman.)



Fig. 909—Comedo with early acneic inflammation enlarged follicle contains lamellated masses of horn walls of the follicle show atrophy, indicating a late phase of the comedo stage; inflammatory reaction is just appearing. (Drs. Eneman and Mook, from McCarthy Histopathology of Skin Diseases, Mosby)

Acne Vulgaris is a cutaneous disease resulting from disorders of lipid metabolism and endocrine glandular balance and characterized by hypertrophy and hyperfunction of the sebaceous glands and by the retention of sebum, inflammatory reaction to which occasions pustulation and necrosis of fat follicles, so that in healing atrophic scars are produced. See Sutton (UCutRev 43 10 1939) Shallow or deep pustules and abscesses are built about and intermingled with comedones. The face is the site of predilection, although the sternal region shoulders and back may be attacked. Lesions may occur wherever comedones may be found. The eruption is symmetric as a rule It is usually limited to areas in which sebaceous glands are normally plentiful and well developed but the scalp is not involved, except occasionally at the occiput, where acne may be manifested as folliculitis cheloidalis. The

sebaceous glands associated with lanugo hair are the ones principally affected. The lesions usually develop rapidly and in crops, and each persists for several days or weeks. While acne papules and pustules may occur on dry skins, oily seborrhea is generally a conspicuous concomitant the integument appearing relaxed dark and greasy



Fig. 910.—Acne vulgaris in a girl. (Drs J A. Fordyce and G. M. MacKee.)



Fig. 911 —Acne vulgaris, severe, cystic case of long standing. (Dr H. C. Varney)

Acne nodules pustules and cysts seem histologically to be foreign body granulomas with leukocytes, phagocytes, and giant cells (Sutton: SouthMJ 34 1071, 1934) The process may affect the superficial part of the sebaceous apparatus so that small acuminate pustules are seen or deeply seated oil depots may be involved, so that the clinical lesion is a deep, tender reddish, sluggish nodule. Deep lesions may become cystic. By extension and coalescence they may involve the conjoined deep portion of several sebaceous glands so as to form painful, boggy tumors Affecting the axillary groin or perianal regions, this disease constitutes one type of hidradenitis suppurativa (q.v) Intergradient types of lesions may occur in the same individual. Hyperkeratosis of the follicular orifice is a recognized feature of comedo formation (Sulzberger et al. NYSJM 34 899 1934) and

perhaps this results in the accumulation of fat in the follicle. In inflammatory lesion Lynch (ADS 42 503 1940) fou d fat mainly in epithelial cells or in lead epithell m but he did not attribute the inflammation to the l pid, a I do (JAm MS 45: 545 1947) The t dies of II es (ArchPath 36: 956, 1153 1106, 1038) of tissue reactions t fatty substances re interesti g and pertinent

Superficial lesions are likely to rupture so as to discharge a more or less solid comedo or the liquid fat representative of it, along with creamy pus. Deep, indurated nodules may eventually discharge; or their soft, greasy purulent material may undergo organization and heal or the contents are phagocytized and carried away or become encysted by epithelium so that a sebaceous cyst forms or the contents are taken up by histiocytes and firm xanthoma like nodules result and these resorb only after many months have passed. What the patient does to the lesions is a variable factor but neurotic excoriation may cause more disfigurement than that due to acné itself

Scarring varies greatly in different individuals. Superficial lesions give rise to little scarring but a full blown lesion results in sloughing out a sebaceous gland so as to leave a pitted scar When lesions are deeply seated abscesses, there ensues more or less destruction with resultant scar formation. In the course of years, disfigurement lessens but it is permanent. Under mining and coalescence of the pathologic process affecting near by follicles result in honeycomb lesions and bridge scars.

Clinical Variants.—Numerous variations of acne deserve mention.

Acne Papulosa is the type in which there re many comedones and some papula in- flammatory lesions.

Acne Pustulosa is comparatively superficial but pustular

Acne Indurata is deeply seated, perhaps secondarily infected.

Acne Cystica may be manifested with only a few or perhaps many deep, cystic lesions containing gelatinous pus.

Acne Cachecticorum is characterized by large soft, purulent, ulcerative, cystic and scarring lesions.

Acne Atrophica.—Comedones and pustules disappear lea ing retiform pitti g a d scarring like folliculitis ulerythematosa reticulata (q.v)

Infantile Acne occurs in the extremely young, especi lly when the ourishment in- cludes too much cream or cod liver oil (Aitken BJD 53: 272, 1942) A n rsing baby with acne had been born with pustules, and ts mother had received bromides, reported Goldsmith (BJD 57 153, 1945) Three cases were reported by Ayres (ADS 14: 12, 1926) 1 by Bel- sario (MJAustral 1 116, 1939) 1 by Traub (ADS 45 809 194) and a newborn by Kikals et al. (ADS 66: 717 1952) Extreme cases in infants have been reported (Ayres: ADS 53: 57 1946), in some of which dremal tumors or hypernephroma ha e been found (Morris: ADS 54: 53, 1946) The disease in infants is the same disease as t is in adults, thought Hellier (BJD 66 25, 1954) after following his infantile cases for years.

Miliary Acne ma ifests numerous pinpoint to pinhead-sized superfi ial, white cysts (T llpan and Zuckerman: MRec 158 670 1945)

Tropical Acne affects the back especially, d velops and disfigures rapidly i person usually of the adult age group, and is apparently caused by hot wet climate (Novy: CalifM 65: 274, 1946; ADS 60: 206 1949; Sulzberg t al.: USNMBull 46: 1178 1946)

Acne Cheloidalis is the type in which keloids evolve about the large, deep comedo es, pustulation being comparatively mild a d the lipoidal foreign substances becoming encased in dense fibrotic tissue. See Folliculitis cheloidalis.

Acné Excoriée is the diagnosis when there are little acne and much neurotic excoria tion. The incidence is common, and the patients are often in their thirties, Wrong (ADS 70 374 1953) pointed out.

Summer Acne of the Extremities.—Small lesions resembling folliculitis are seen itchy nd rem niscent of the acneic eruption from testostero e occurring in both males and females. I fi d these cases responsi e to the red ction of ingestion of milk nd to the admi istration of estrogen e hormones

Acne Keratosa was described by Crocke (BJD 11: 1 1899) on the basis of 4 cases in w men with f generall sized, w ll-defined, excoriat d patches covered with hard blood stained rust situated on the cheeks and chin, especi lly near the angles of the mouth with se m f ld lesions. A lesion commences as a firm, red, tender lump, on which a pustule usuall f rms d dries i t a scab, and this is remo ed by the patient, who has an irresistibl desire to squeeze r pick out soft or horny conical plugs that are embedded in the kin gl ing rise t great irritation until they are remo ed. I look on this fai ly rare disord r as form f eurotic e coriation closely allied to delusion of parasitism (q.v)

Symptomatic Acne (Acne Artificialis) develops from xtrinsic causes. Bromide and iodide rashes resemble acne (Sulzberger t al.: NYSJM 34: 899 1934) Iodized salt has been alleged as a cause, as has bromine vapo Occlusion of the follicula orifices by oils

or paraffin is an etiologic factor and is often seen among workers in binding-twine factories (Mayers and Silverberg: JIndustHyg 20: 244, 1938); see Oil acne, a disease that may result also from the use of paraffin hair oil (Berlin: AIH 69: 653 1954). Vaseline and Hallrer oil may cause eruption of small acneic lesions (Pét r: J 10: 532, 1934). Masculinizing adrenal tumors often provoke acne (Kepler et al.: PSMMC 13: 2..., 1938) as may injections of androgen (Hamilt n: JClinEndocrin 1: 570, 1941). Acne caused by testosterone is usually widespread, follicular and itchy. See Dermatitis medicamentosa, ACTH, androgen, bromide, cod liver oil, iodide, progesterone.

Acne Conglobata is a chronic inflammatory disease of the skin which is characterized by the presence of the constituents of acne vulgaris, including comedones, papules, and pustules, and in addition large elevated fluctuating plaques which are dusky blue and frequently form cutaneous or subcutaneous abscesses and oil cysts, which may perforate and form discharging sinuses, healing very slowly and often leaving keloidal or so-called bridge scars (Brückennarben) of Lang (Michelson and Allen: ADS 23: 49 1931). The lesions closely resemble tuberculodermas of the colliquative type or scrofuloderma. The clinical description and course of acne conglobata place the disease in close relationship to dermatitis papillaris capillitii and to perifolliculitis capitis abscedens et suffodiens. The difference from ordinary acne lies in the autoinoculability of acne conglobata, a fact which does not prove that the lesions are not inflammatory reactions to lipid, just as acne lesions are. The boy reported by Pautrier (AnndeD 5: 233 1934) had banal acne which rapidly changed so that the lesions became purplish, torpid, swollen ones, with fistulas and seropurulent exudate and they spread to new areas and were vegetative and indolent. No lymphadenitis was present.

Etiology.—Blood cultures were negative in the 2 cases of Belote (ADS 27: 302 1933) but from aseptically opened abscesses, there were obtained *Staphylococcus aureus* from 1 and *S. albus* from 2; from ulcerous lesions only *B. coli* was found. There were no agglutinins for either staphylococcus. Belote believed the patient himself the factor and a variable one at that, but neither *M. tuberculosis* nor any other specific organism underlies the disease. Pautrier like Belote believed that the cause lies in the terrain, not the flora. I think of acne conglobata as representative of extremely severe acne with multiple comedones which are confluent beneath the follicular orifices and productive of large cystic lesions and bridge scarring.

The disease may be limited to axillary or perianal distribution and so comprise one variety of hidradenitis suppurativa (q.v.; see Sutton and Marks: J 1*) 1344 1943; Mark: SouthMJ 39: 4 7 1946). Cases occur almost exclusively in males over 20 years of age and may remain active for many years (Gent: DWchr 111: 983 1940). See Hoffman (ArDuS 150: 134 1926; ZentralblHHuG 19: 1, 1926). Interesting reports, suggestive of the interrelationship of acne vulgaris, acne conglobata, perianal pyoderma and hidradenitis suppurativa, include those of Diamond and Laufman (AmJDigDis 8: 25.., 1941); Jackman (AmJDigDis 9: 220, 194); Wolf (ADS 46: ..9 194) and O'Leary et al. (ADS 47: 725, 1943).

Treatment.—Pautrier's patient slowly responded to treatment with baths, camphorated alcohol, iodized alcohol and roentgen therapy. Hot baths with green soap and an ointment of sulfur and salicylic acid were successful but gold therapy was not beneficial in the case of Michelson and Allen. Recommended for these rare cases is the trial of a low fat diet and the administration of thyroid; estrogenic substances may help, as reported by Forman (BJD 60: 333 1948) whose patient was benefited by the implantation of a 300 mg. tablet of stilbestrol. Antibiotics may control secondary infection but have proved, in my experience, basically ineffectual, for the disease is not primarily a parasitic one. Mere incision and drainage requires endless repetition, but radical surgery with plastic repair may succeed in managing cases affecting limited regions. Exteriorization of the undermining lesions was recommended by Duemling (ADS 52: 75 1945) and Bereston and Benteen (ADS 56: 7 1947) in suitable cases.

Acne Varioliformis, considered to be essentially a staphylococcic folliculitis, is described with disorders affecting the sebaceous glands.

Colloid Acne.—A rare variant of acne in which the lesions, scattered irregularly over the cheeks, are yellow, transparent and colloidlike was described by Brocq (Précis atlas de





Fig. 912.—Acne vulgaris. (Drs. Forsythe and MacKee.)
Fig. 913.—Scarring from cne. (Drs. L. R. Pels nd J. W. Lord.)





Fig. 914.—Neurotic excoriation superimposed on acne causes most of the disease. (ebl

pratique dermatologique Doin et Cie 19?1 p. 11?6) The lesions are secondary to acneic eruptions, which fact together with their distribution differentiates them from colloid milium. They feel soft and spongy When they are punctured, a yellowish, jellylike substance followed by a drop of blood can be squeezed out. Greenbaum (ADS 8 416 1923) recalled Jullusberg's hypothesis that colloid milium represents a secondary manifestation of a pre-existing condition a scar or granulation tissue in which the products of elastic tissue degeneration predominate, and suggested that colloid acne may be closely related to colloid milium (q.v.) if not identical with it. Greenbaum (ADS 39: 382, 1939) thought the disorder simply the degeneration of acne lesions, and by no means rare The lipid being liquid, comedones are not formed.

Etiology and Pathology of Acne—Comedones occur at any age they usually develop during the adolescent period. Factors in the production of comedones are disturbances which tend to increase the activity of the sebaceous glands. Greasy skinned individuals of the so-called seborrheal type are predisposed The epidemiologic study of Hinrichsen and Ivy (ADS 37 975 1938) showed no sex preference but acne appears a little earlier in girls, in association seemingly with their earlier sex maturation. The incidence diminishes in men after age 19 but clinical acne is common even after age 30 (Forbes BJD 58: 208 1946) This is true also of women (Cohen BJD 57 10 1945) Constipation, dyspepsia fatigability anemia and menstrual derangements are frequent concomitants these are also symptoms of hypothyroidism and estrogen imbalance

Heredity is responsible for a predisposition to acne (Stokes and King ADS 26 456 1932 Hellier BJD 51 109 1939) It is the physiologic background necessary for the development of acne which is inherited (Stryker and Bloom SouthMJ 31 741 1938) and the changes become manifest with the physical and biochemical alterations of adolescence The disease has been met in only one of a pair of identical twins (Pusey and Rattner ADS 29 705 1934)

When acne is localized as it often is in the region of the chin or sometimes on one side of the face a postural habit or a habit of fondling the skin of that location is likely to be in part causative (Stokes and Garner J 93 438 1929) Stokes and Sternberg (ADS 40 345 1939) gave an instructive analysis of etiologic factors, including an evaluation of the causes of relapses.

The ill effect of emotion and the unfortunate influence of the disease upon emotion concerned Marshall (CanadMAJ 44 509 1941) The distress suffered by the patient resulting from his disfigurement, from the sluggishness caused by his endocrine imbalance and from the cruelty of those who accuse him, openly or by innuendo of being unclean and lazy deserves sympathy Regarding etiology the psychosomatic approach merits direct quotation "Is it not conceivable that these patients project their presumed internal badness on their body surface either with the unconscious intention of ejecting it in the manner of an excretory process, or on a much more superficial level as an act of confession? (Wittkower: BJD 63: 14 1951)

Acne developed only in the bald regions in a case of alopecia areata, a most unusual phenomenon reported by Ringrose and Ekblad (ADS 66 22, 195?) This could have been oil acne from previous self medication, regarding the possibility of which the authors gave no data.

Exacerbations occur during intercurrent illnesses and often shortly prior to menstruation (Stokes and Callaway ADS 36 976 1937) Iodides make acne worse

The blood iodine levels of acne patients do not differ from controls (Traub and Emmet ADS 41 506, 1940) It is unnecessary to limit the ingestion of ordinary iodized salt in treating acne (Gaul and Underwood ADS 58: 439 1948)

Corynebacterium acnes has been suspected of being the cause of acne but no one ever caught acne and pus from the lesions is innocuous. Vaccines of *C acnes* are therapeutically worthless (Fleming Lancet 1 1035 1909 Costello and Washburn ADS 38 45 1938)

The organism is not pathogenic for various laboratory animals however "Some experimental results have been presented which suggest that the acne bacillus plays an active role in some of the lesions of acne vulgaris passively as a foreign protein if not as an infectious agent (Ketron ADS 15 568, 1927 Ketron and Brown ADS 20 815, 1929) The assumption of Bloch (BJD 43 61, 1931) that inflammation implies infection on account of his overlooking the fact that the inflammatory phase of acne is foreign body reaction to lipids, a tuberculoid reaction which has caused pathologists to confuse acne with tuberculosis (Veress: DWchn 107: 1519 1938) and which is the result of reaction between sebaceous ma

Fig. Fig. 815.—Atrophic scars from severe acne. (Dr. G. C. Dennie.)

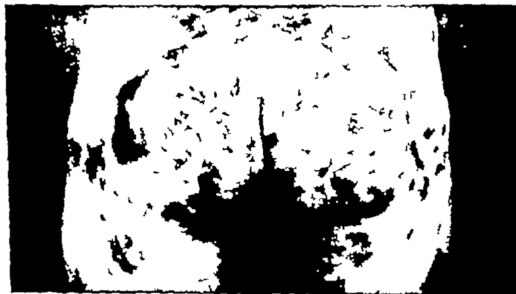


Fig. 816.—Acne conglobata. (Dr. F. Ronchese.)

terial and the mesodermal portion of the skin. It is a type of inflammatory reaction which has nothing necessarily to do with infection but which results from bruising a comedo, or from injecting comedo material intradermally or from injecting any other waxy material into the skin, as Smithburn and Sabin (J Exper M 56: 867 1932) did with chemical fractions of *M tuberculosis* and as other investigators have done with other oily substances (see Foreign body granuloma)

If a comedo has once formed it like a deposit in xanthoma cannot easily be resorbed, but it can slowly be phagocytized The process of phagocytism probably is instigated by a failure of the epithelial wall separating comedo lipid from living connective tissue The breach can come from trauma as in the case of bruised comedones or milia. Perhaps it depends generally on an endocrine failure of fat gland epithelium to maintain its integrity The breach is that which distinguishes affliction with mere comedones from acne vulgaris.



Fig. 917 —Acneic inflammation in deep cystic case granulomatous and foreign body reaction to sebum is seen in the vicinity of the arrector pili muscle (Photomicrograph by Dr Fred Weidman)

Foreign body reaction to comedo material may take place shallow or deep Phagocytosis may attack solid well-saturated lipid or liquid, fairly unsaturated fat. The clinical picture varies with the location shallow or deep and with the violence of the inflammatory processes, which may be sluggish or active The result may be (1) discharge of oil by rupture of a pustule or (2) slow resorption of oil by phagocytosis or (3) enduring imbibition of oil by fixed tissue elements so that a xanthomaform keloidlike scar persists or (4) epithelium may grow around the oil separating it from the tissues capable of inflammatory response so that a cyst results The cyst wall may fail after a time so that a quiescent lesion becomes an inflamed one Hyperlipemia needs *to be only temporary* as in xanthoma to result in lipid deposit and to produce excess seborrhea and additional comedo material, and so to provoke a new

crop of acne pustules. Clinicians see exacerbations of acne follow the ingestion of a single dish of ice cream The inflammatory response is not immediate but is delayed some 24 to 48 hours, like other tuberculoid responses.

Acne vulgaris is to be defined as the disease which consists in tuberculoid inflammatory reaction to sebum which is excessive through the subject's improper metabolism of lipid. It is a kind of pustular lipidosis. In contrast with mesodermal lipidoses (xanthomas) acne vulgaris is a primarily epidermal lipidosis, with secondary inflammation It appears to be dependent (1) on the excessive dietary intake of oil of which milk, milk products and pork are abounding sources; (2) on hormone influences, through the function of endocrine glands in the control of fat chemistry thyroid function being itself related to other endocrine apparatus and their balance and on the androgen-estrogen balance; (3) on vitamin intake through (a) the need for vitamins in maintaining epithelial integrity and through (b) the antagonism between carotene vitamin A and thyroxin and (4) on iodine, (a) in the excess of which hyperlipemia occurs, counterbalanced by thyroxin unless this is itself deficient, and (b) in the absence of which the thyroid gland cannot function successfully Sensitivity to iodide on the part of the patient with acne is due to his hypothyroidism give the patient iodide *and* thyroid extract in adequate amounts and he does not suffer eruption.

Yet one finds patients who are still seborrheic despite low fat diet while taking correctly balanced doses of thyroid and estrogen, which tend to diminish the size and activity of sebaceous glands (see Seborrhea) More factors exist than are known at this time. Patients who do not respond well to treatment based on these interpretations are persons whose oil flow is liquid and whose pustules are either very superficial tiny and thin walled or are deep xanthomatoid and not benefited by incision. These same patients are not much helped by roentgen therapy either See Seborrhea (p. 669)

NUTRITIONAL AND BIOCHEMICAL CONSIDERATIONS.—On a high-carbohydrate diet 10 patients in hospital became better not worse Crawford and Swartz (ADS 33 1035 1936) reported. Menagh et al. (JMichMS 37 521 1938) found diminished carbohydrate tolerances in 70% of their cases and reduced B.M.R.s in 65% they gave insulin to the 1 group and thyroid to the other with beneficial effects for the most part, but they disregarded diets. White (J 103 1277 1934) and Cormia (JAllergy 12 34 1940) knew that some acneiform eruptions depend on foods and can be cured by elimination diets, and that they are not distinguishable by skin tests. In avitaminosis A (q v) there is a supplanting of follicular and glandular epithelium by keratinizing squamous epithelium so that follicles become plugged, secretion is diminished and the skin is dry Acne appears in avitaminosis A with noteworthy rarity (Lowenthal ADS 28 700 1933) but acne can be caused by taking fish oils to excess. Thyroid function is necessary for the metabolism of fat (Hurxthal ArchIntM 53: 762 1934) and in hypothyroidism, hyperlipemia is present. Milk, cream ice cream meat and chocolate are the commonest fat rich foods, and they cause comedones and acne when ingested in amounts beyond a person's metabolic capacity The balance between the intake of lipid and its management when absorbed dependent as its metabolism is on endocrine function, is the balance which determines seborrhea and the formation of comedones, I think.

Cholesteremia is not concerned (Strickler and Adams: ADS 26 11 1932; Lewinn and Zugerman JLabClinM 28: 190 1942) Kalz (JID 17 273 1951) reported that the serum lipids of 34 acne patients were not significantly different from normal before or after a test fatty meal their increase of lipid after the meal being within normal limits. The cholesterol esters were significantly lower and the free cholesterols were higher in his acne patients than in controls. He tabulated the total serum lipids in 50 acne patients, whose average was 690 mg % and in 10 normal controls whose average was 616 mg % The difference between these averages, 74 mg % is 12% in excess of the average normal figure Curiously he did not consider this significant I (JMoMA 49 471 1952) administered cortisone experimentally

to 3 recalcitrant cases of acne. In 2 of them with marked hyperlipemia previously unresponsive to thyroid cortisone reduced the total serum lipids and temporarily improved the acne, but not to a great degree. In 1 without hyperlipemia cortisone was without even temporary beneficial effect. It is pertinent to note that cortisone suppresses the adrenal production of androgen.

When the acne patient on a low fat diet drinks milk new lesions appear in about 36 hours, the time required for fat to be deposited and tuberculoid inflammation to develop. Lipochrome pigments are significant as well for catsup and excessive orange juice have as bad effects as butterfat.

I have seen exacerbations follow the ingestion of skimmed milk by patients who had been getting on well when they drank no milk but were after a time allowed skimmed milk so that protein and calcium intake might be increased. Since milk comes from a modified fat gland I wonder whether it contains a water-soluble hormone which increases the activity of sebaceous glands.

The inverse ratio between blood cholesterol and the function of the thyroid gland was demonstrated by Epstein and Lande (ArchIntM 30 602, 1922). In hypothyroidism cholesteremia is increased, while in hyperthyroidism it is diminished. Hurxthal (ArchIntM 52 86, 1933 53: 762, 1934) demonstrated the fact that blood lipid studies are more reliable in assessing thyroid function than are determinations of the basal metabolic rate. Clausen (J 111 144 1938) gave a detailed review of the physiologic properties of vitamin A, including its antagonism to thyroxin.

Hyperkeratosis of the epithelium at the mouth of the follicle is the first step in comedo formation it is generally agreed. Unna ascribed the blackness of the outer tip of the plug to chemical changes in the excreted material for it is not dirt but it can be bleached. Owing to the pressure atrophy when adjacent glands are involved a single chamber with multiple ducts may result. A double or triple comedo (Ohmann Dumesnil) and similar lesions occur as a sequel to tissue destruction in suppurative lesions (Duhring). The so-called bottle bacillus is commonly present and in addition to this organism, other micrococci particularly *Staphylococcus aureus* and *albus* are found in the lesions. *Demodex folliculorum* is also a frequent inhabitant of the plugs.

Hyperkeratosis at the mouth of the follicle is due to irritation, hypothesized Sulzberger et al. (NYSJM 34: 899 1934) and this is the first step in comedo production the "concentration of irritants" in the comedo accounts for the inflammatory reaction. Reaction is inevitable if normal, living mesodermal tissues come in contact with sebum, and they do when trauma damages a comedo-containing follicle, or when the epidermal wall of a cyst undergoes pressure atrophy or when the epithelial membrane separating sebum from mesodermal tissues becomes discontinuous. Sulzberger et al. proposed seeking abnormal constituents of sebum this would seem unnecessary for sebum itself provokes acneiform inflammation when the epidermal barrier is defective. But consideration of the facts elucidated by Hass (ArchPath 20 956 1935), regarding tissue reaction to lipids, suggests that abnormal constituents may be concerned. The reaction to unsaturated fatty acids, particularly those from cod liver oil, is much more violent than to saturated fatty acids. One needs also to inquire why there is so much sebum, and why it gains access to the reactive mesodermal elements.

Potassium iodide 3 drams of 8% in water given each day for 2 weeks made worse all patients with acne vulgaris and only 1 control patient of Sulzberger et al. (1934). This is not an allergic reaction in the ordinary sense. Sodium chloride in large doses had no effect on their patients, nor did patch tests yield positive results. Sodium chloride intravenously however in doses of 50 to 300 cc. of 1% solution, greatly helped the cases reported by Goodman (AD&S 31 828, 1935). Administration of iodide increases cholesteremia a little in acne patients (Turner and Steiner JClinIn 18 43 1939).

Fats from the skin surface were not found to be different in acneic persons and controls by Kile et al. (AD&S 61 792, 1930).

ENDOCRINE INFLUENCES.—The age of onset is coincidental with sex maturation and is somewhat earlier in girls (Hinrichsen and Ivy IllMJ 74 85 1938). A statistical study of 2,136 girls and 2,155 boys of Zurich, the severity of whose acne was carefully graded on the basis of enumerations of comedones and pustules, indicated that acne is a young person's disease is a real dyshormonal dermatosis, and shows predilection for thick-skinned persons of dark pigmentation (Bloch BJD 43 61 1931).

Pick (ArDuS 151: 350 1931) reported correlation of acne with hormonal influences and, in his treatment of 17 cases with gonadal extracts, obtained best results in cases associated with rosacea. Cunningham and Lunsford (CalifWM 35: 22, 1931) examined 5,000 women and discovered no differences between those with and those without acne, in nutrition, incidence of constipation, o menstrual derangements. Wolf (Endocrinology in Modern Practice, Saunders, 1936 pp. 64 733) believed that an endocrine factor is in most cases of prime importance, and that perhaps because of haphazard diagnosis or insufficient therapy many attempts to allay acne by hormone therapy have proved to be failures or only partial successes. Hypothyroidism wa associated with 3 of every 5 cases, he stated, and thyroid and gonadal medication often proved efficacious in clearing the skin. Van Studdiford (ADS 31: 333, 1935) believed that hormone therapy is hopeful when it establishes glandular balance and serves to regulate the menses.

Estrogenic substance, assayed by the Frank and Goldberger method, was diminished in quantity in the blood of girls with acne tested by Rosenthal and Neustaedter (ADS 32: 560 1935) Estrogenic substance in 50 R. U doses and pregnancy urine hormone in 100-unit doses were given, in alternated courses of 5 intramuscular injections at daily intervals, to 38 women and 2 men by Rosenthal (JLancet 56: 496, 1936) Determinations of the amount of estrogenic substance in the blood of these patients showed that 62% f the women were subnormal in this respect. Of the 40 patients, 23 were improved to greater or lesser degree.

Lawrence (J 106: 983, 1936) knew that endocrine imbalance is somehow in olved in acne, and he helped some patients by giving antuitrin-S, a careful assay of the value of which was made by Williams and Nomland (J 109: 564, 1937) who gave measured doses to a controlled series of 28 girls and 11 boys averaging 19 years of age. Their study revealed no bad reaction, no effect on menstruation, and no detectable improvement when 5 700 rat units were given intramuscularly 3 times a week fo 8 to 11 weeks. Testosterone propionate was given by Molitch (Endocr 23 803, 1938) by intramuscular injection on alternate days to 13 of 23 young white men, and the remaining 10 received injections of only the sesame oil vehicle; after the course of treatment, both groups had improved slightly and equally and he could account for improvement only on a psychologic basis.

An oversupply of male sex hormone may be concerned (Wile et al.: ADS 39: 195, 1939) although increase or diminution of androgen excretion has not been proved in either sex. Lawrence and Werthessen (Endocr 27: 755, 1940) reported disturbance f androgen-estrogen ratio. The 1 ketosteroid excretion in 26 patients tested by Quiroga et al. (Mod 5: 347 1950) proved to be excessive in both sexes. Ketosteroid excretion in young men with acne was measured and found to lie within the normal range, reported White et al. (USAFMJ 3: 131 1952) No significant increase in androgen excretion was found by Becker (ADS 67 173 1953) In neither males no females were the urinary levels of 17 ketosteroid ex cretion different from normal in the investigations of Kooij et al. (Dermatologica 109 175, 1954)

Many older studies have been concerned with attempts to control acne vulgaris by the use of various hormonal substances, with irregular unsatisfactory and unpredictable results; see Cohen (BJD 53: 231; 269 1941)

Both progesterone and testosterone, given to rats, induced increase of the size of fat glands by as much as 400% reported Haskin et al. (JID 20: 207 1953) The ill effects o acne of both hormones are seen from time to time in my practice.

Hormonal therapy such as has been summarized here has missed the point, it seems to me of the need for balance between diet, metabolism, autogenous hormonal activity and medicinally supplemented hormone substances. Cases are individual. A small proportion of them, if their sebace ous structures have not been deformed by aimless routine therapy can be managed with success solely by diet and extraction of comedones. Some require thyroid extract in addition to dietary limitations, some need estrogen, some need both hormones. Correct dosage is essential and individual. If x ray therapy is instituted *after* diet, local attention and hormones have been used for 2 months, then the response to x ray is striking and prompt, for then is the time when its necrobiotic effect on sebaceous glands is logically most applicable and actually most effective See Acne treatment endocrine therapy (p 690)

Other Factors.—Although no support for a hypothesis that psychiatric factors are of etiologic significance could be adduced by Cohen (BJD 57: 48 1945) there are reasons to disagree The output of sebum from the skins of acneic patients was measured under normal and stress conditions by Wolff et al. (TransAssnAmPhys 64 435 1951) who reported an increase ranging from 200 to 500% resulting from angry emotional reactions. Exacerbations of acne were observed to follow emotional reactions by from 24 to 48 hours, and the

disease was quieter during periods when the patients lives were tranquil. One frequently sees school children whose faces are clear during the vacation months and relapse when the pressure of educational and social activities becomes heavy

No significant relation between seborrhea, dandruff and acne was found by Cohen (BJD 57 45 1945) there was no association with hypertrichosis (BJD 57 102, 1945) but heavy sleeping and the failure to feel refreshed by sleep occurred in patients of both sexes (BJD 57 147 1945) confirming an observation of mine of symptoms I attribute to hypothyroidism for they disappear when the correct dose of thyroid is established. Studies of the BMR of 353 patients by Smith et al. (JID 17 13 1951) revealed abnormally low results in 160 and results above plus 10 in only 8

Prognosis.—Acne vulgaris is an obstinate and spontaneously scarring disorder prone to relapse and to recur Perseverance in good treatment is usually followed by acceptable improvement however and this disease typically of adolescence sometimes disappears spontaneously as the years go by Niles (ADS 27 89 1933) indicated that the amount of scarring in acne vulgaris is largely dependent upon the severity and duration of the disease and *is neither increased nor decreased by roentgen therapy* Treatment which prevents the development of new lesions and which curtails the suppuration of inflammatory ones is best Evacuation of pustules if properly done lessens the scars which might be expected.

Treatment.—It is probably true that no 2 dermatologists give the same instructions and carry out the same therapeutic procedures in acne (JID 3 143, 1940) In this presentation which endeavors to correlate theory and practice I emphasize my own views It appears scarcely debatable to state that acne represents a glandular disorder wherein the sebaceous glands are the seat of clinically conspicuous dysfunction. Sebum accumulates within enlarged glands or their ducts. Inflammation of the foreign body type appears about the sebum Purulent sloughing follows, and pitted scars spontaneously ensue. If parasites appertain to this process, they serve only as secondary invaders, and this they may be but the hypothesis has long been laid to rest that acne is primarily a manifestation of parasitism. It is a chemical, metabolic, glandular abnormality

If the fat glands of the acneic patient could be got small and empty he would no longer have acne The aim of making the glands small and empty can often be achieved by the following measures

(1) external cleansing with soap or detergents, a superficial effort which helps a little, maybe but which if pursued with vigor will bruise and injure sore tissues;

(2) dieting eliminating especially milk, ice cream, chocolate nuts and an excess of the lipochrome pigment substances of oranges and tomatoes; this helps quite a bit but does not of itself assure a cure

(3) administration of hormones

(a) thyroid, which helps greatly in many cases but not in all, its benefits being attributable to its influence on fat metabolism, although this effect is probably not a full explanation and

(b) estrogenic substances, as detailed in the final paragraph on endocrine therapy (q v)

(4) x ray therapy which yields dependable improvement, to be attributed to the secretion influence of radiation on glandular epithelium and on the elements of inflammation

(5) topically applied astringents and exfoliating agents generally incorporating sulfur; these have I think, quite limited virtue, being variously assessed by various authorities and

(6) evacuation of pustules and extraction of comedones, the minor surgery of acne, which is indubitably beneficial if skillfully done but which cannot be more than palliative in that, while debridement gets sebum out of the skin, thereby anticipating the foreign body reaction to it, surgical effort cannot prevent the reappearance of the irritating lipids, unless it destroys glandular epithelium.

There are further measures which can be used to the advantage of certain acne patients. I have used them and evaluate them from first hand knowledge:

(7) giving an iron, vitamin and liver extract preparation such as Perihemin or Redicyte and this seems often to be really helpful (Sutton, Sr [ADS 18: 887 1928] recommended liver therapy and Marshall [JID 205, 1939; MinnM 23: 796, 194_] has been keenly interested in this aspect, and Kutapressin, the S-factor of liver extract, was reported upon favorably by Burks and Knox [ADS 70 506, 1954] although I have no confidence in it)

(8) eliminating focal infection, a measure useful i some cases where secondary parasitism is troublesome; and finally

(9) combatting secondary parasitism with

(a) an attack upon seborrheic dermatiti of the scalp, prescribing for example a salve to be applied overnight once a week and removed by shampooing the next day containing 3% sulfur and 5% salicylic acid in Carbowax 1,500;

(b) an attack upon bacteria internally with such agents as penicillin by injection (Mitchell Heggs: Practitioner 157 379 1946) or Terramycin, Achromycin, Erythromycin or such by mouth (Becker and Fredricks: AD 72 157 1955);

(c) an attack upon bacteria externally with an antiseptic—an effective mixture is Vioform Cream with 1.0 Gm. sulfur and 200 mg chloramphenicol per ounce to be rubbed gently into the skin at bedhour nightly or less frequently if it irritates.

Local Treatment of the comedones and pustules is delicate and exacting minuscule surgery which must be performed by the physician the patient being prohibited from picking at his lesions. The purpose of local treatment is to get rid of lipid depots before they provoke inflammation or with as little trauma as possible after they have done so.

Removal of comedones is important and it must be done gently without crushing particles or droplets of lipid into surrounding tissues. The uninflamed comedo is often bulbous, so that a tiny episiotomy (from the mouth of its follicle outward along the line on the skin of the geometric projection of its slanting axis) enables one to pop it out without applying undue pressure. A V may work better than a slit I use thumbnails, not comedo extractors. A pair of strong convex spectacles or a low power binocular dissecting microscope makes the local therapy of acne more accurate and satisfactory It is a jewler s job and a tedious one but the results of meticulous attention repay the pains. An inflamed comedo must be treated exceedingly gently If, after slitting the follicle it does not come forth readily it is better let alone than bruised. Solid lipoidal collections are far more easily removed than liquid ones, and a cold pack is a more suitable preliminary in cases of low melting point seborrhea than the hot pack which makes it easier to remove solid comedones. The pustule containing a semidigested comedo must be slit open *just widely and deeply enough to let out the contents of the pustule or cyst.* Skutta (DWehn 102 137 1936) proposed a suction device, which he claimed gave excellent results; I have not seen it.

Deeply seated cystic inflammation is best let alone unless there is an obviously thinned, reddish area through which discharge is about to take place spontaneously Such lesions will generally resorb in time and they are not helped by anything one does to them. To incise them repeatedly or to excise them results in an unsightly scar for which the physician is not thanked.

Monopolar electrodesiccation of milia and comedones was done skillfully enough by Nomland (ADS 48 302, 1943) to obtain good results in 25 of 31 cases.

Traditionally one prescribes a sulfurous astringent such as lotio alba

℞	Phenol	1.0
	Zinc sulfat	1._
	Sulfur precipitated,	
	Sulfurated potash	_0
	Rose water	to 180.0

Diluted Vleminckx solution as a hot, moist pack was a favorite of Wise (NYSJM 33 1321 1933) A complex sulfur preparation in a penetrant wetting agent vehicle (MacKee et al. JID 6 309 1945) has been highly recommended. Dobes (SouthMJ 44 546 1951) incorporated Intraderm Sulfur with CO_2-acetone slush Trying several different topical applications, Clyman et al (ADS 62 441 1950) found one no better than another I prescribe none

Ultraviolet light is temporarily helpful in mildly peeling dosage. A hazardous topical application containing coal tar and sulfathiazole intended to induce photosensitization, was devised by Kurtin and Yontef (NYSJM 48 1606 1948) and received amazing publicity

To peel the face with a powerful agent may be undertaken only under closest supervision it is dangerous and violent and does not have lasting beneficial effects (Eller and Wolff J 116 934 1941 QMRA J 122 1277 1943) I have had no experience with the phenol method advocated by MacKee and Karp (BJD 64 456 1952) A technic of peeling the skin was given by Urkov (IllMJ 89 75 1946) but citation does not imply recommendation

Cryotherapy popular impressive and temporarily beneficial through its peeling effect (Karp ADS 39 995, 1939) is accomplished by grinding solid CO_2 in a mortar with acetone to make a slush, which is quickly swabbed over the affected parts (Dobes and Keil ADS 42 547 1940) Its defatting and exfoliating influences are creditable but its value in amelioration of scars is at best dubious (Friedlander ADS 46 734 1942) Zugerman (ADS 54 209 1946) used ethyl acetate as the vehicle and added sulfur to the refrigerant. Freezing individual pustules with solid CO is often helpful (Wright and Gross ADS 59 664 1949)

An individual scar may be reduced in conspicuousness by electrocoagulating after local anesthesia, the edges in such a way as to smooth the lesion (Hartman ADS 66 123 1952) Kurtin used ethyl chloride freezing as a preliminary to planing down the edges with a motor-driven metal brush a method tested and approved by Monash (J 149 1078 1952)

See Eile (NYSJM 54 1166 1954) Elan and Rein (ADS 70 784 1954) history technic results Reiches and Lakeles (MoMed 52 183, 1955) motor-driven, stainless steel brush, the Kurtin plastic planer technic and indications Burks (SouthMJ 48 452, 1955) brush technic with refrigeration may be used for pigmented nevi and other blemishes.

The plastic surgical effort utilizing general anesthesia for abrasion with sandpaper is applicable onl in selected cases (McEvitt J 14 : 64 1950 Beerer GP 9 66, 1954) The operation is time-consuming only a part of the face may be attacked at one time repeated hospitalizations with attendant expense and consumption of time are necessary and the resultant thinning of the skin is somewhat objectionable A moto -driven burr may be so applied as to reduce excesses of connective tissue at chosen sites (Kromayer 1909 cited by Reiss J 154: 536 1954) and was described as employed in treating tattoo and nevi by Led g (DWehn 1?4 317, 1951) *Surgical planing* was discussed in detail b Kurtin (ADS 68: 389 1953) Its applicability is more limited than the current enthusiasm for its use the propriety of which presupposes that the operator be neither unskillful nor unscrupulous.

A plastic surgeon can insert a pad of fat under an atrophic scar (Downing ADS 24: 1063 1936) o pull the skin of the face taut by exci ing tissue from w th n the hairline These methods may be expected to yield only temporary improvement.

Roentgen Therapy produces necrobiosis and atrophy of sebaceous follicles but does not influence the cause of sebaceous hyperactivity Roentgen therapy will not rid the dermis of embedded comedones and waxy cysts, which must be removed mechanically It may be relied upon to improve a higher proportion of patients than any other single agent (King and Hamilton JTennMA 34 272 1941 Smith TexasSJM 38 512, 1942) It is generally not advised for patients under 16 years of age Given on only one side of the face it seemed to Kline and Gahan (ADS 46 207 1942) to help both sides. It is not the sole agency for treatment (Twining PaMJ 44 1165, 1941) but works especially well in conjunction with appropriate dietary and endocrine therapy Exacerbation, sometimes explosive, may follow its use in cystic cases (Michael ADS 27 96 1933) MacKee (X rays and Radium in the Treatment of Diseases of the Skin Lea & Febiger 1938 p 416) recommended doses of 75 r each week at 80 to 100 kv most patients will tolerate 3 or 4

months of this without atrophy he stated but after 4 months one *must* stop Fair and pustular patients may tolerate only half as much. The danger of resultant permanent injury must be continually borne in mind, but the safety of radiation in skilled hands is undoubted. None of 58 patients who received therapy from 6 to 25 years previously showed radiodermatitis reported Crawford et al. (NEngJM 245: 720 1951) who claimed best effects from dosage totaling from 1,000 to 1,200 r given in an uninterrupted series. No sequelae were noted by Sulzberger et al. (ADS 65 630 1952) from doses of 1 000 r or less, while no sequelae of consequence followed dosage up to 1 400 r Belisario (MJAustral 2 656, 1935) recommended ¼ E given 8 times, while Miskjian (OhioSMJ 37: 1177 1941) preferred doses of 150 r given each 2 weeks to a total of 8. The need for x ray therapy diminishes as improvement in dietary and hormonal therapy progresses, and Andrews (Diseases of the Skin, Saunders, 1946 p 234) was already making less and less use of it.

GENERAL MEASURES.—One should discourage free sweating for to sweat is to secrete also an increased quantity of sebum (Cleveland CanadMAJ 38 481 1938) Adequate sleep is desirable, for chronic fatigue is certainly a harmful influence. Sexual tension is undesirable but is often unavoidable One sees acne disappear after marriage and reappear along with neurotic excoriation, after divorce Focal infections must be eliminated in some instances, for tonsillectomy may work wonders in a severe and difficult case (Andrews ConnMJ 13 309 1949)

Tonics may be employed, such as the venerable I.Q and S. or the more modern iron and B complex pill. Marshall (JID 2 205 1939) recommended a liver extract and it helped some of the patients of Lichtenstein and Stilliana (ADS 45 959 1942) Riboflavin, useful in rosacea, may help here Viosterol in doses of 20 000 to 100 000 units daily (Hinrichsen and Ivy IllMJ 74 85 1938) has been followed by improvement in many patients and harm in few (Maynard ADS 41: 842, 1940) Large doses of vitamin A were recommended by Straumford (NoWMed 42 219 1943) but my experience agrees with that of Lynch and Cook (ADS 55: 355 1947) who were unable to confirm him. Patients given large doses of vitamin A by injection by Mitchell and Butterworth (ADS 64 428 1951) for the most part got worse Pyridoxine, from 25 mg b.i.d. to 50 mg 5 times a day yielded benefits in many cases, reported Jolliffe et al. (JID 5 1943 1942) Acne is not a vitamin problem but when vitamins are needed in any condition, their administration is helpful.

Penicillin, tetracycline and other antibiotics benefit secondarily infected and painful acne; they can at best subtract only the infectious moiety of the patient s disease

Foreign protein therapy has largely been relegated to history

The reduction of emotional tension a feat seldom achieved by the efforts of the physician is often followed by notable improvement. Teenagers with acne often clear up during the summer months of vacation from school and relapse after the fall classes are resumed. Some patients who are overloaded can to their advantage be induced to do less and sleep more Beauty sleep the clinician may call it, when he wants a girl to follow his advice

DIET —Taking into account the noninfectious nature of the disorder the greasiness of the skin and evidence that acneic inflammation is tissue reaction to lipid, I hold it advisable to see that the patient does not take much oil in through his mouth so that he cannot put much out through his skin. I prescribe therefore, a low fat diet which may contain as many calories as the patient can swallow If he ingests fewer calories than he consumes, he loses weight for the calories he burns but has not ingested must come from his own stores of fat. Therefore a diet on which the patient loses weight is not a low fat diet, and patients losing weight do not show improvement. To accomplish low fat nutrition the patient must be on a high protein, high-carbohydrate diet. In designing any diet, the tables of Chatfield and Adams, U S. Dept. of Agriculture Circ. No 549 are useful. In general, foods of vegetable origin are low in lipid content, and foods of animal origin are oily

LOW FAT ADEQUATE DIET FOR ACNE PATIENTS

Instructions.—A diet to be followed for a long time must be adequately nutritious, easy to follow and fit to eat. There is no restriction of quantity eaten. Do not go hungry. Keep a record of weight. This is not a diet for allergy wherein 100% of certain items are interdicted.

Eat sugar, sugar candy (without nuts or chocolate), bread and cereals, vegetables, fruits (with minor restrictions as to orange, grapefruit, tomato), meat of any kind, fowl, fishes.
Do not drink milk. It is allowed on cereals and in the cooking in moderate amounts.
Do not eat any ice cream, chocolate, nuts, popcorn, potato chips.
Observe the following limitations:

Coffee, tea, cola beverages—1 cup a day, total
Orange—One a day (orange juice is limited);
Grapefruit—One half a day (grapefruit juice is limited);
Tomato—2 slices a day (tomato juice, catsup and soup are limited)
Butter—One modest serving with each meal allowed
Cheese—No limit on cottage cheese, but oily cheeses are like butter;
Egg—One a day allowed.

Do not restrict your diet more than you are told to.

Some acneiform eruptions of the face are due to foods and can be cured by means of elimination diets stated White (J 103 1277 1934) but the offending foods cannot be detected, he believed, by means of skin tests. The diet prescribed by Sulzberger (VaMMonth 65 381 1938) was not intended to eliminate either fats or carbohydrates but rather certain foods, oftenest chocolate, to which the patient was allergic. Exacerbations caused by foods were interpreted as sensitivity phenomena by Cormia (JAllergy 12 34 1940) who thought chocolate, tomato, nuts, spinach and wheat to be frequent offenders. Flood (PaMJ 51 533 1948) limited the ingestion by his patients of milk, pork, chocolate, tomato, orange and nuts, which he interpreted as allergenic. Milk intolerance in children is often a symptom of unrecognized hypothyroidism according to McLendon and Jaeger (SouthMJ 36 671 1943).

Endocrine Therapy.—Thyroid extract enhances lipid metabolism and regularly lowers lipemia. Clinical indications that thyroid is needed include the following: the patient lacks vigor, never feels slept out despite having been abed for what should be a sufficient length of time, requires an alarm clock to wake up, lacks an appetite for breakfast, perhaps ingests a great amount of caffeine (giving thyroid-like stimulation, masking the sense of fatigue), gains weight easily, tends to be constipated, has menstrual periods which are delayed, irregular, of less than the usual 5-day duration, fails to become pregnant despite adequate opportunity to do so. Anemic individuals not responsive to adequate iron, vitamin and other nutritional therapy are often hypothyroid. Such persons, when they have acne, manifest improvement in, or return to normal with respect to, all these symptoms when dosed with thyroid correctly; see Kimball (KyMJ 1 468 1933), Rose (PaMJ 43 752, 1939), Wharton (CanadMAJ 40 371 1939), Wilkins (J 114 2382 1940), Christman (OhioMJ 46 965 1950).

The correct supply of thyroid must be that of a normal person, in whom any additional thyroid is too much. I seek to dose the acne patient so that he resembles the normal in that more thyroid would overdose him. The correct dose is found by experiment: placing the patient on 1 grain U.S.P. with breakfast each morning it is easy to discover whether this dose is (1) too little and does nothing, (2) too much and poisons the patient, however mildly, or (3) just right. I am like perhaps half of all internists in disregarding the B.M.R., in which I have neither confidence nor interest. Some regard may be given to the basal temperature obtained by holding an accurate thermometer in the mouth for 5 minutes prior to arising and reading it to the tenth of a degree. A temperature below 97.8° F suggests that thyroid may be increased a trifle, but at 98.2° F overdosage symptoms are present or imminent (Barnes, J 119 1072 1942). The maximum tolerated dosage is *just less than* that which produces *any* symptom of overdosage.

Indications of overdosage include nervous tension, insomnia and restlessness, headache dizziness weakness, tremor palpitation, and/or continued loss of weight. Milk is the antidote for thyroid overdosage, as sugar is for insulin. At the *first* appearance of any symptom of intolerance the dose is diminished to a tolerated level. This necessitates keeping the patient under strict supervision seeing him each week recording his weight, inquiring of him how he tolerates the medication and making suitable adjustments of dosage.

When a patient takes thyroid for two weeks and makes no response of any kind, he is underdosed. When a patient on a given dose manifests improvement in symptoms such as waking readily and desiring breakfast when previously he did not this dose is a correct one and a larger dose will likely lead to overdose symptoms.

Correctly administered, this regimen of diet and thyroid medication can not be harmful. As soon as a proper level of thyroid intake is established, seborrhea and inflammation greatly diminish in most cases. The diet is strict at first and is broadened as the disease is controlled, until the patient discovers how much fatty food he can ingest without erupting The earliest article I have found on the use of thyroid in treating acne was by Chalmers (abs JCutD 31 694 1913)

The imbalance of hormones other than thyroid plays an important etiologic role but how much of which hormones to give and under what circumstances are difficult questions. There is accumulating evidence that estrogenic substances are dependably helpful.

The great value of estrogenic therapy nowadays becoming recognized, has been stressed by Goeckerman (ADS 61 237 1950) and Goeckerman and Wilhelm (ADS 66 402 1952) It is necessary to give enough but missed periods or excessive menstrual flow is an indication of overdosage as are also nausea and nervous tension.

Premarin is a popular estrogenic substance and is the one I use. I start with a dose of 0 3 mg daily and keep accurate records of the date and duration of the periods and the effects, if any on attendant cramping, tenderness of breasts and premenstrual flares of acne Rarely a dose as great as 1.25 mg per day appears necessary Most patients need only 0 3 mg per day Some patients do better when the dose is given from the time of ovulation until the end of the next flow and is then withheld until the next ovulation. Some acne patients do not need it at all See Sutton (ADS 70 462 1954) I doubt the virtue of applying estrogenic hormones topically for the effect seems to me to be systemic by absorption rather than local, and percutaneous administration can yield only inaccurate dosage. Premarin lotion was strongly recommended by Shapiro (J 156 1470 1954)

In the se re cystic type in males, I followed in 1948 the recommendation of Bell sano to give 1 mg of stilbestrol daily for week o two in a course desisting when the pples become sore and, in gi ls, to give the natural estrogen in aqueous suspension during the first 3 weeks f the cycle in modest dosage which helped the skin as well as b-normalities of menstruation in some cases. Injections of an extract of the urine in preg ancy were ported by Lawrence and Feigenbaum (NEngJM 21 ; 1 13, 1935) to have cured 8 of 15 cases. Such a gonadotropic substance wa beneficial nly in some of the papulopustule cases of McCarthy and Hunter (ADS 35: 211 1937) who were disappointed with h rmonal therapy at that tim Rosenthal (NYSJM 37: 44 1937) obtained some improvement with estrogenic substances. Improvement was obtained in some patients, both male and female using Emmenin, Hollander and Schmitt (PaMJ 43: 49, 1939) found. Diethylstilbestrol, 0.5 mg per day helped most, reported Lawrence nd Werthessen (JClinEndocrinol 3 636 1943) Not much good came of pregn nt mare' serum in the experience of Birnberg and Bein (JClinEndocrinol 4: 63 1944) Stilbestrol appeared well worth giving, thought Scott (BJD 56: 36, 1944) Stilbestrol 1 mg. daily and thyroid 1 gr daily w re recommended by Mitchell Heggs (Pract 157: 379, 1946) Stilbestrol in a dose f 1 or 2 mg. per day resulted in significant depression of the urinary excretion of 17 ketosteroids, White and Lehmann (ADS 65: 601, 1952) found, but their acneic patients did as w ll without the chemic l as they did with it.

Recognizing the endocrine pathogenesis of c , Goldzieher (MRec 160: 725, 1947) felt that the effectiveness of estrogenic substances lay in their ability to suppress the

secretion of androgen. He discussed the ill effects, which might involve gonadal damage or upset of the menstrual cycle. These disadvantages may be dismissed, now with current recognition that estrogen if given wisely does no lasting harm to the male and a temporarily upset menstrual cycle in a girl is inconsequential, although she and her parents may require reassurance. In fact some patients do not do well until estrogen is pushed to the point of inhibiting ovulation and preventing the formation of corpora lutea so reducing the production of progesterone which has effects on sebaceous glands resembling those of testosterone. The menstrual flow then represents only anovulatory bleeding, but there is no reason to believe that such a state of affairs, if not maintained too long is ultimately detrimental.

Andrews et al. (J 146 110, 1951) either would administer diethylstilbestrol 0.25 mg., more or less, daily or would administer one or more capsules daily containing diethylstilbestrol 0.25 mg and thyroid 8.0 mg (⅛ grain) along with cascara and sodium bicarbonate. Their report stressed the value of estrogenic therapy and played down the value of thyroid, while they depreciated the utility of x-ray therapy. In my opinion ⅛ grain of thyroid is an insignificant daily dose. If a patient needs thyroid at all, he needs at least 4 to 8 times that much. Sutton Sr., many years ago might have accredited the cascara content of the Andrews acne capsule with significant powers. The constipation of acne patients responds to thyroid properly given (Sutton: JKansMS 48: 545, 1947. 49: 471 193-)

The patient who improves on estrogen is generally the girl whose milia are deep whose pustulation is comparatively scanty whose skin is dry and looks as if vitamin A might help (but it seldom does) and whose response to thyroid yields less than the expected improvement. Reliable indications that estrogen is needed and will be beneficial are the girl's menses last for 6 days or more instead of the normal 4 to 5 days they are accompanied by cramps during the first day or so the breasts are sore (not merely engorged a bit) just before the periods and her acne undergoes exacerbation a few days before the periods. If the woman feels tired yet has a desire for breakfast, which the hypothyroid individual cares little about and if thyroid given tentatively proves not tolerated estrogenic substances are likely to be helpful.

With estrogenic substances in the male patient my experience and confidence are increasing and one may prescribe them stopping the dose when the nipples enlarge and become tender and resuming it when the breasts return to normal with a fair likelihood of securing some diminution of fat gland overactivity

Estrogenic substances applied topically and absorbed percutaneously gave noteworthy results, reported Zondek (SchweizMWschr 65: 1157 1935), and these findings were confirmed by Shapiro (ADS 63: 224, 1951) Inunction of estrogenic substances applied to rabbits resulted in percutaneous absorption and reduced the size of the sebaceous glands, reported Ebling and Gellis (JID 1 169 1949) the effects being reversible when the hormone was discontinued. The opposite resulted from the inunction of testosterone. Premarin Cream was applied locally by Sawicky et al. (ADS 63 17 1953) appearing to be especially helpful in deep cystic acne of males. I suppose that estrogenic substances may as well be given by mouth as through the skin and am dubious of any advantages that topical administration may have. Injections need not be given.

Desiccated adrenal substance was given orally by Pusey and Rattner (ADS 31 845, 1935) with favorable results in those patients whose dysmenorrhea was helped.

Insulin has been tried: Wortis (J 108 971, 1937) reported speedy improvement induced by hypoglycemia, and a few cases of Semon and Herrmann (BJD 51 477 1939 52: 123 1940) appeared to be helped by doses not exceeding 10 units twice a week.

See Delmarto (MJAustral 2 16, 1953) individualization of treatment using topical, mechanical, dietary and endocrine measures, Didcoct (JID 23 243 1954) irregular temporary benefit with cortisone, Morris (ADS 70 363 1954) citrus juices helpful Aron-Brunetière (AustralJD 2 114, 1954) endocrine studies, necessity for correct dosage Newman and Feldman (ADS 69 584 1954) premenstrual one of the type undergoing remission during pregnancy responsive to progesterone given 10 days before periods Jarrett (BJD 67 165, 1955) benefit with stilbestrol given orally producing significant reduction of surface sebum; Moore (CornMJ 19 93 1955) systemic and topical treatment including estrogens topically

DERMATOLOGIC ASPECTS OF ENDOCRINE DISTURBANCES

Addison's Disease—Atrophy dysplasia calcifying tuberculosis or other destructive alteration of the adrenal glands results in disease, usually of insidious onset, early manifested by asthenia and dizziness on change of posture. Anorexia and nausea follow later irregular crises occur with collapse dehydration, hypoglycemia and hypotension, and death is imminent in these. The course of the disease when untreated is usually progressively downward

with acute exacerbations at irregular intervals and spontaneous remissions which may persist for weeks or months while an occasional patient appears to recover spontaneously (Rountree et al. J 96: 231 1931) Melanin pigmentation of skin and mucosae is common, may appear early but is not necessarily present in which cases diagnosis may be difficult (Parker PSMMC 10 344, 1935) Its intensity ranges from light to almost black. It is diffuse but is deeper on exposed parts and intensifies normal pigmentation. The neck flexures and regions affected by acanthosis nigricans are the site of predilection. Over the diffusely pigmented skin there may be little mole like spots of deeper pigmentation, and upon the trunk, particularly on the lower abdomen, it may be ribbed like the sand on the seashore (Osler and McCrae Medicine Appleton) The mechanism of the pigmentation is obscure

Adrenal Cortical Insufficiency is recognized by the characteristic changes in the clinical picture and diagnostic blood chemical findings of high urea and potassium and low chloride and sugar (Sigland PSMMC 22 17 1947) The patient is perched on the brink of a physiologic volcano (Conference on Therapy J 112 2011, 1939) Diagnosis of crisis is suggested by marked prostration, hypotension hiccups and signs of circulatory collapse. The 24-hour urinary excretion of 17 ketosteroids is diminished the finding of more than 4 mg in women or 10 mg in men tends to exclude Addison s disease as the diagnosis. Restriction of sodium chloride intake provokes indications of adrenal insufficiency while this is a dangerous procedure, it may be performed for diagnosis (Cutler et al. J 111 117, 1938 Willson et al AIntM 69: 460 1942) When the adrenal cortex is deficient, it cannot, of course respond to stimulation by purified pituitary adrenocorticotropic hormone when the adrenal cortical reserve is adequate, the injection of 25 mg of the pituitary hormone is followed by a decrease of 50% or more in the urinary uric acid creatinine ratio (Thorn et al J 137 1005, 1948) Such a decrease does not occur in Addison s disease Nor does ACTH produce a fall in the number of circulating eosinophils to the extent to which it does in normal persons (Best et al J 151 702 1953)

The chemical similarities of sex hormones desoxycorticosterone and related substances of notable physiologic activity were interestingly presented by Mason (PSMMC 15 289 1940)

Treatment with high-salt, low potassium diet and desoxycorticosterone acetate starting with 50 mg subcutaneously per day is effective (Thorn and Firor J 114 2517 1940) Pellets of the steroid may be implanted under the skin so that gradual absorption meets the patient s need (Thorn et al. BullJHH 64 339 1939 Engel et al. AnnIntM 17 585 1942) The technic of implanting the hormone was described by Firor (AnnSurg 111: 942, 1940) The low potassium diet was given in detail by Sister Mary Victor (PSMMC 12: 404, 1937) foods especially rich in potassium include avocado, pear banana, currant lime and rhubarb With appropriate doses of DOCA potassium restriction does not need to be meticulous for the drug greatly aids in the retention of salt and water (Tooke and Kepler PSMMC 15 365 1940) but overdosage results in edema, hypoproteinemia and cardiac embarrassment (Ferrebee et al. J 113 1725 1939)

Cortisone given orally in conjunction with the use of DOCA is effective and valuable (Levy J 140 411 1952) Cortisone half of a 25-mg tablet b.i.d., helps the Addisonian sufferer immensely Transplantation of adrenal tissue from another person may have cured a patient (Broster BMJ 2 750 1940 see Edit J 113: 1034 1939) With successful treatment, pigmentation may diminish or disappear Acute hemolytic streptococcic complications are not unusual, but may be expected to respond to sulfonamide therapy (Thorn and Lewis J 118 214, 1942)

See Rosoff (J 106 279 1936) Addison's disease caused by surgical denervation of adrenals in therapy of diabetes Green (AIntM 59 759, 1937) 34 cases and historical review Hendel and Seibl (CanadMAJ 39 457 1938) case due to amyloidosis in pulmonary TBC; Hampton and Kepler (AmJMedSci 202 764, 1941) 110 Mayo cases, with evidence of TBC in 17; Thorn et al. (AnnIntM 16 1053, 1942) rehabilitation of half of 158 cases treated with DOCA, TBC causal in less than half; NNR (J 140: 838 1949) DOCA structure, action,





Fig. 918.—Acanthosis nigricans [illegible] eyelid and lips. (Dr A. J. Markley.)
Fig. 919.—Acanthosis nigricans, involving lips. (Dr William Frick.)





Fig. 920.—Acanthosis nigricans. (Dr M. Jessner.)
Fig. 921.—Acanthosis nigricans: hyperkeratotic and pigmentary palms changes. (Dr William Frick.)

cases Simpson (JClinEndocrinol 9 403, 1949), case in diabetic, Anderson et al. (JClinEndocrinol 9 1324, 1949) oral administration of DOCA; Bolinger (J KansMS 51 273, 1950) technic of evaluating adrenal cortical function O'Donnell (AI CM 86 236, 1950) etiology and necropsy findings; Uroen et al. (NEngJM 244 471 1951) licorice therapy, Wallach and Scharfman (J 148; 729 1952) case due t drenal metastases of bronchogenic carcinoma)

Acanthosis Nigricans is a disease of chromaffin tissue insufficiency first described by Pollitzer (J 53 1369 1909) in 1890 The dermatologic manifestations comprise melanin hyperpigmentation and papillomatous hypertrophy affecting the axillae neck, genitalia and groins, face medial thigh, antecubital and popliteal regions, about the umbilicus and anus, and, often, the oral and genital mucosae Constitutional symptoms include asthenia, hypopiesis, loss of weight anorexia, hypometabolism, decreased 17 ketosteroid excretion and diminished serum sodium and chloride concentrations as in Addison s disease (Thorn J 125 10 1944)

Juvenile and adult cases have been distinguished the juvenile being usually benign in etiology and the adult depending generally on tuberculous or neoplastic destruction of the adrenal and retroperitoneal chromaffin tissues. Some juvenile cases are associated with obesity which is usually of the pituitary type (Robinson and Tasker ADS 55 749 1947) Curth (ASurg 47 517 1943) reported benign and malignant cases entirely similar insofar as



Figs. 822 and 823.—Acanthosis nigricans. (Dr C. J White)

skin changes are concerned. Half of the cases are cancerous in origin. The division of types should be into (a) those associated with malignancy and (b) those not associated with malignancy wrote Curth (ADS 66 80 1952) rather than into juvenile and adult types. See Curth (J 157 266 1955)

Skin changes have been known to precede the recognition of cancer by 6 years, and they precede the diagnosis of cancer in about 20% of the cases. They sometimes regress when the cancer is treated and relapse when it recurs. The benign type usually appears before or during puberty Familial cases occur and these are usually benign. The spread of skin changes after puberty is a bad omen. The skin lesions are usually symmetric in malignant cases, and when asymmetric, which is rare, the case is usually benign.

The disease is comparatively rare. Cutaneous lesions may develop slowly and insidiously or rapidly The earliest manifestation is usually hyperpigmentation the affected skin assuming a reddish, brownish or blackish hue which gradually fades off at the margin. The epidermis becomes thickened, but without accompanying induration, and the natural lines of the skin are exaggerated. These changes are followed by the development of numerous soft, millet seed to pea-sized, papillary growths. These little tumors are often accompanied by crops of warty papules which are distributed irregularly over the hands, forearms and thighs. There is generally more or less associated

hair loss, particularly of the scalp and eyebrows, and the nails usually become striated and brittle. *Hyperkeratosis of the palms and soles is a common accompaniment.*

The benign type can occur at birth develop in childhood or appear at puberty. It is accentuated during adolescence and thereafter remains stationary or regresses. Benign and malignant types are Curth thought, to be considered different disease entities.

Malignant cases are generally associated with adenocarcinoma, which may arise in any of various organs, and have been related to cancer in the stomach or abdomen in 85% of the cases, in the breast, lung and elsewhere in 8%. The cancer is always highly malignant, and all instances have proved fatal, usually within 1 year after diagnosis.

The onset was sudden in an old woman with esophageal cancer reported Cochrane and Alexander (BJD 63: 225, 1951) who found no dysfunction of the adrenals and who obtained benefit with respect to skin lesions by giving vitamin A. The buccal mucosa may be thickened and velvety or granular in appearance, or it may be the site of numerous small, papillomatous growths. Only the absence of papules and verrucous lesions differentiates Addison's disease from acanthosis nigricans. Eleven cases each of the benign juvenile and malignant types were reviewed by Kierland (JID 9: 299 194) who noted that the histologic features of early acanthosis nigricans resemble those of normal axillary skin.

A pseudo acanthosis nigricans may occur in the body creases of obese brunette persons, noted Curth (195?) This condition apparently depends on factors accompanying obesity because it develops when the patient gains weight and disappears when he loses it. Pseudo acanthosis nigricans should be differentiated from true acanthosis nigricans so that patients may be spared the needless anxiety of believing they have a cancer related disease and so that a rational system of treatment may be instituted.

Supportive measures and rest are indicated. Various extracts of adrenal cortex have proved successful in replacing the deficiency as in Addison's disease q v Treatment directed at encompassing hormonal balance was discussed by Curth (1952) orchiectomy cured a benign case of Hellerstrom (ActaD-V 14 86 1933) and estrogen helped one of her own patients.

See Dubreuilh (AnnDerm 7 47 1916) case, gastric cancer with skin changes overlying skin metastases Mukai (ActaD-V 14 469, 1933) of 193 cases only 1 associated with malignancy occurred in a patient under 20 years of age, while 50% of patients over 40 were associated with malignancy Miescher (HandbHaut, Springer 4, pt. 2 372, 1931) review to date, 212 cases Grace and Schwartz (ADS 28 481 1934) oral pigmentation in half the cases, Addisonian but with papules, and verrucous lesions ? same in ½ of cases Masson and Montgomery (AmJObGyn 32 717 1936) 13 cases, Herold et al. (ADS 44 789, 1941), female, 17 with gastric cancer no demonstrable adrenal cortical dysfunction; Nicholas (ADS 44 318, 1941) old woman with retroperitoneal lymphoblastoma, Levin and Behrman (ADS 48 84, 1943) pulmonary cancer; Hollander (ADS 48 836, 1943) female 38, with gastric cancer, Kaufman and Smith (ValMonth 74 284, 1947), female, 8, with no demonstrable adrenal cortical dysfunction Kaufman and Tilley (NEngJM 238: 320 1948) female, 11 with cancer of thyroid Ellenbogen (BJD 61 251 1949) 3 cases on record in cancer of lung; Hoffmann (J 186 342 1954) case, juvenile type, with pituitary basophilism Sheldon and Curtis (AD 72 63 1955) juvenile case with pituitary hypogonadism and diabetes mellitus

Acromegaly due to pituitary dysfunction with excessive production of growth-stimulating hormone by the eosinophilic anterior lobe cells, is characterized by hypertroph of the bones and soft parts, particularly of the face and the extremities. The onset of the disease is insidious and its course progressive. The parts affected by predilection are the face, particularly the lower jaw the malar bones, the supraorbital prominences and the distal ends of the extremities, although no region is exempt. Cardiac failure is common in sufferers with acromegaly (Courville and Mason AIntM 61: 704 1938)

Cutaneous changes include thickening and furrowing, seborrhea and comedo formation, coarse and wiry hypertrichosis and, often, areas of pigmentation. Epidermal, glandular and collagenous hypertrophy, and pigmentation of the rete are found (Simpson: BMJ 1: 937 1936) The nails participate in the general hypertrophy becoming broad, striated, sometimes spoon shaped (Wiener: Skin Manifestations of Internal Disorders, Mosby 1947 p. 290). Enlargement of fingers and toes, furrowing of the forehead skin and periostitis, without elongation of bones, typical skull or jaw changes or cessation of progress after age 25, were described as "acropachyderma with pachyperiostitis by Brugsch (AIntM 68: 687 1941). Compare Cutis verticis gyrata, and Pituitary basophilism.

Hypopituitarism (Hypophyseal Cachexia)—Simmonds disease is characterized by emaciation, amenorrhea, hypogenitalism, hypotension, hypoglycemia, low basal metabolic rate asthenia, dental caries, atrophy of the mandible and generalized pigmentation (Wilson: BMJ 1: 814 1936) Weakness, loss of normal hair increase of hair on the face slow pulse and anemia are also observed. The patients seemed to undergo speedy senility and they died.

True hypopituitarism is the result, as a rule of postpartum hemorrhage into the pituitary gland (Cooke and Sheehan: BMJ 1 928, 1950) Glinski described the disease accurately in 1913, correctly attributing it to necrosis of the pituitary according to Robertson (BMJ 1: 921, 1951) It is characterized by fatigability and symptoms suggestive of myxedema, with weakness, pallor anemia, scant eyebrows and the absence of pubic and axillary hair Reviewing the records of 95 cases of long standing and proved by demonstration at autopsy of major losses of pituitary gland tissue, Sheehan and Summers (QuartJMed 18: 319, 1949)





Fig. 924.—Acromegaly in a woman 51 years old. (Meakins Practice of Medicine, Mosby.)

Figs. 925 and 926.—Acromegaly (Dr. Ralph Major.)

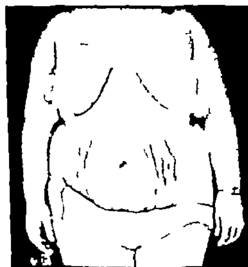




Fig. 927.—Cushing's syndrome in a girl 15 years old. Amenorrhea since age of 12, obesity, striae glycosuria, blood cholesterol 269; normal eye grounds (Courtesy the late Dr. Ware; from Wiener Skin Manifestations of Internal Disorders, Mosby 1947.)

Fig. 928.—Myxedema note thickness of lips, puffiness about eyes, scanty hair and dull expression. (Meakins Practice of Medicine, Mosby.)

hair loss, particularly of the scalp and eyebrows, and the nails usually become striated and brittle. Hyperkeratosis of the palms and soles is a common accompaniment.

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fluence is traceable in some cases. The loss of fat involved the face, neck and trunk of the patient reported by Watson and Ritchie (QuartJMed 18: 224, 1925). It involved the face, arms, trunk and thighs of that of Christiansen (RevNeurol 38: 1169, 1922). Fat disappeared from the whole trunk and thighs of the boy reported by Leipoldt (SoAfrMJ 15 161, 1940). A stocking-like loss extending up to the thighs was the condition of the girl described by Bigler (J 11 : 627 1939). Murray (BMJ 2: 1236 1952) reported 3 cases, 2 of which were classic and 1 was of the Laignel-Lavastine and Viard type, wherein the loss of fat from the upper part of the body was slight but obesity below the waist was pronounced. He collected 74 cases from the literature among which glycosuria, hepatomegaly and insulin resistance found in his 2 typical cases, were rarely mentioned.

Diabetes Mellitus.—Cutaneous manifestations include those due to dehydration and to dysfunction of metabolism of vitamin A and carotenoid pigments (q v). Eruptive xanthoma and necrobiosis lipoidica have been described elsewhere. Lamb and Kaltz (JOklaMA 34: 93, 1941) reviewed these conditions and discussed also pruritus, which may be generalized or localized to the genital region, insulin allergy (dermatitis medicamentosa, q v) and susceptibility to tinea, secondary infection furuncles and gangrene (q v). In experimental animals, injections of aceto-acetoacetic acid and cholesterol did not induce itching (Koenigstein: JID 10: 285 1947).

DIABETES OF THE SKIN was postulated by Urbach (J 129: 438, 1945; see Urbach and Lentz: ADS 52: 301 1945) in a patient whose intracutaneous sugar concentration seemed not to parallel that of his blood, an "independent cutaneous glycohistechia. The clinical picture was of furunculosis, sweat gland abscesses, eczema and pruritus, responsive to low-carbohydrate diet with or without insulin. Submitted as proof was a solitary point on the dotted line representing the skin sugar content at the third hour in Urbach's chart 1.

Diabetes Insipidus.—Mild pruritus, dry skin, xerostomia and lack of sensible perspiration were described by Brayton (J 43 377 1904).

Hyperthyroidism.—The blood lipid is low and the administration of iodine or thyroidectomy results in rise of the cholesterol level (Man et al.: JClinInv 19: 43 1940). The skin is warm, flushed, moist and free from acne. The hair tends to be thin and of fine texture and the nails thin and fragile. Pruritus is sometimes annoying. Multiple telangiectases have been described. Pigmentary changes, patchy or generalized, may develop. Erythema of the chest and back may be seen, and hyperhidrosis is sometimes troublesome and weakening (Wiener, 1947). The red streak following scratching of the skin is more marked and longer lasting than in the normal (Marañon's sign). Vitiligo occurs in perhaps 10% of the cases of Graves' disease. Transient edema, puffy eyelids and chronic urticaria are common.

The Cutaneous Mucoid States were classified as (1) cutaneous changes in true myxedema (a) classic myxedema (b) skin changes associated with low BMR but without myxedema, and (c) local or general cutaneous myxedema associated with rare endocrine disturbances (2) localized circumscribed usually pretibial myxedema, almost invariably associated with exophthalmic goiter and (3) lichen myxedematosus (q v) wherein no relation to disturbance of the thyroid or other endocrine glands is apparent (Montgomery and Underwood JID 20 213 1953).

MYXEDEMA is due to extreme thyroid insufficiency. The onset is usually gradual with anemia, weariness, depression, irritability, mental listlessness and characteristic cutaneous changes. The skin becomes dry, rough and yellowish. Though swollen, it does not pit on pressure. There is mild dandruffy scaliness, and sweat secretion is diminished. The cutaneous regions commonly affected are the face, particularly the lips, nose and eyelids, and the neck and hands. The swollen, masklike face, everted lips, expressionless eyes and pudgy hands combine in an appearance which is distinctive. Volar hyperkeratosis is a common symptom. Pigmentation in myxedema is more marked on exposed surfaces, especially the forehead and cheeks, and is seen on the extensor aspects of the forearms but to a lesser degree on the neck, abdomen, calves, axillae and inner aspects of the thighs; it does not occur in the mouth or on the tongue (Kranz and Means BostonM&SJ 95 518 1926). Conversion of carotene to vitamin A is impaired by thyroidectomy (Drill and Truant Endocrinol 40 259 1947). The skin changes of myxedema may occur in trypanosomiasis (q v).

The skin of the cretin is cool, dry and bronzed or pasty white and shows disturbances in the amount, texture and distribution of hair, while disturbances of the nails are minor, observed Butterworth (ADS 70 565 1954). He found that cretins tolerate cold poorly and are hyporeactive to cold pressor tests. Their tolerance of ultraviolet irradiation is above normal, yet less pigmentation develops following exposure than in normal individuals. Histo-

logically Butterworth noted thinning of the epidermis and dermis, sparsity of the epidermal appendages, hyperkeratosis, prominence of the granular layer fragmentation and shattering of collagen bundles and fibers, and striking degeneration of elastic tissue Mucoid changes however, were not outstanding While some of the clinical and microscopic changes respond to thyroid therapy others are degenerative and permanent.

Neonatal jaundice may indicate at an early age the existence of congenital myxedema (Akerrén abs J 157 1583, 1955)

Cretinism turns out badly despite opotherapy Marvel (ActaPediat 24 214 1939) reported in a study of 16 cases followed for from 6 to 32 years. The stature remained subnormal and the intelligence low

Mild Degrees of Hypothyroidism are common, and in adolescents the condition is often associated with acne (q v) Hypothyroidism interferes with metabolism of lipids, including carotene and vitamin A. Cutaneous lesions comprise only a part of the widely distributed myxedematous changes. The B.M.R. may or may not be lower than normal (Mason RockyMtMJ 36 399 1939) The patient may be fat or thin and the thin hypothyroid child may be nervous and hyperkinetic (Rose PaMJ 42 752, 1939) Anemia, constipation, menstrual disorder usually in the form of delay and scantiness, occasionally with excessive flow and sterility are among the symptoms. Lack of energy drowsiness and failure to be refreshed by sleep are typical (Kimball KyMJ 31 488 1933) The diagnostic criterion is the response to thyroid therapy (Wilkins J 114 2382, 1940) Blood fat is affected the hypothyroid individual being hyperlipemic (Boyd and Connell QJM 6 467 1937) but cholesterol may be normal while total lipid is significantly elevated (Radwin et al AmJDisChild 60 1120 1940)

Administration of thyroid causes blood fat concentration to diminish toward normal overdosage causes diminution to subnormal levels.

The psychiatric features, including psychomotor retardation, fatigability irritability and depression, were of especial interest to Akelaitis (JNervMent Dis 83 22, 1936)

Unusual hirsutism in 4 hypothyroid children disappeared after a few months of thyroid therapy noted Perloff (J 157 651 1955)

Mild hypothyroidism is a common geriatric difficulty not always recognized but productive of weakness depression and vague aches and pains. Administration of thyroid to aged persons is at least as often beneficial as the administration of androgen or estrogen Hashinger told me

Circumscribed Myxedema —In the skin 2 types of circumscribed myxedema were recognized by Pillsbury and Stokes (ADS 24 255 1931) those with nodular papular or diffusely infiltrative lesions distributed on the face arms back and scrotum and those with similar lesions on the shins. The disseminated type may respond to thyroid medication the commoner pretibial type does not. The 8 cases of O'Leary (ADS 21 57 1930) were associated with hyperthyroidism as is usual, and with chronic edema of cardiac decompensation the lesions were nonpitting tawny plaques on the legs. Clearing followed biopsy in one of O'Leary's patients, and it was noted by Grals (JID 12 339 1949) that following incision, a lesion drained for some 2 weeks then healed the skin returning to an almost normal state In the case of Dossekker (AfDuS 123 76 1916) the implantation of thyroid tissue obtained from a patient with Graves's disease resulted in recovery

Histologically one finds mucus infiltration of the cutis and immature connective tissue cells, or star cells (Reuter: ADS 24: 65, 1931) The cause is unknown and treatment has been unsatisfactory it being unusual for the lesions to disappear even when the presumably etiologic toxic thyroid is removed (Handley and Downing: ADS 40: 374, 1939) The basic abnormality seems to be related to that of progressive exophthalmos in Graves's disease where edema and cellular infiltration increase the volume of the retro ocular structures; similar alteration in heart and skeletal muscle tissues is produced by injecting the thyroid stimulating hormone from the pituitary Curtis et al. (ADS 60: 318, 1949) pointed out in presenting 5 cases exhibiting the coexistence of local myxedema and exophthalmic goiter

Localization of myxedematous changes in tissues other than the skin was discussed by Marañon (PresseM 46: 1417 1935) Evidence indicating that a considerable portion of the swelling in circumscribed myxedema consists of the mucopolysaccharide, hyaluronic acid, was adduced by Pulitz and Brunner (JID 14: 159, 1950) who classed the mucinoses as those of metabolic type influenced by endocrine mechanisms, and those of catabolic type representative perhaps of mucinous degeneration of connective tissue and seen in sarcoma, fibroma and lipoma. It was argued by Asboe-Hansen (JID 15: 25, 1950) that the increased substance in the connective tissues is hyaluronic acid, for it can be caused to diminish in quantity by injections of hyaluronidase (Bloom et al.: JID 12: 339 1949; Grais ib. p. 345)

See Ingram (BJD 45 19 1933); Netherton and M Ivaney (J 104 1492, 1935); Sandbacka Holmstrom (ActaD-V 17: 547 1936); Marchionini and Jahn (ArDuS 176 694, 1938); McEwen BMJ 1: 1037 1938); Downing (ADS 41 422, 1940); Schwartz and Madden (ADS 43 375 1941), Becker and Rothman (ADS 46: 321, 1942); Sonneri (ADS 48 70, 1943); Netherton (ADS 48 123, 1943) Amersbach and Kanee (ADS 49 415, 1944); Cohen (BJD 58 1 3, 1946) with bibliography; Freudenthal (BJD 59: 288, 1947) unusual case involving face Green and Freudenthal (BJD 60 22, 1948) antecubital location, simulating Schweninger Buzzi disease





Fig. 979.—Myxedema tuberosum. (Original of Dr M. Jessner from Wiener: Skin Manifestations of Internal Disorders, Mosby 1947)

Fig 980—Circumscribed tuberous myxedema. (Division of Dermatology Department of Medicine, University of Chicago from Wiener Skin Manifestations of Internal Disorders Mosby 1947)

Lichen Myxedematosus (Papular Mucinosis) may be described as generalized localized myxedema not associated with thyroid disease, according to Dalton and Seidell (ADS 67 194 1953) whose studies of their patient were intensive. In this woman, new lesions as they developed were yellowish shiny dome-shaped, rounded papules of from 1 to 5 mm. in diameter They occurred singly in annular patches or in linear array and were sometimes grouped around pre-existing striae The older lesions became dull, pinkish and sometimes coalescent. The arms and forearms, buttocks and legs were the principal locations. Theirs was the most extensive case on record, noted Cole (ADS 67 208 1953) who commented on the normal BMR, which is usual and the absence of response to thyroid.

The disease usually occurs as a generalized lichenoid eruption and less frequently in discrete papules or lichenoid plaques, rarely urticarial (Montgomery and Underwood: JID 20 213 1953) It differs from other types of

myxedema in not being associated with demonstrable endocrinopathy and is of unknown pathogenesis. The lesions are characterized by the deposits of large amounts of mucin, identified by the mucicarmine stain and located in discrete areas in the upper cutis.

Hyaluronidase digested the material in Dalton and Seideli's case and the clearing phenomenon was manifested for biopsy was followed by resolution of the lesions in the immediate vicinity. No other means of treatment was availing.



Fig. 931.—Lichen myxedematosus. (D. John E. Dalton.)

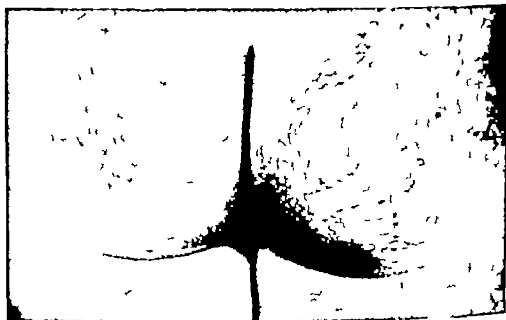


Fig. 932.—Lichen myxedematosus. (Dalton and Seidel: ADS 67 104, 1953.)

The injection of hyaluronidase into the lesions of the patient of Langer and Paschel (Ztsch H g 13 33 1952) provoked the disappearance of soft ones but not hard ones. Cortisone and ACTH were unavailing in the case of Donald et al. (AustralJD 1 23, 1953). The case of Butler and Lawson (ADS 33 919 193) exemplified an int relation with scleroderma, and e lesions h as l he ruber moniliformis (p. 914) may be concerned with comparable mesodermal degenerative processes.

See Dubreuilh (AnndeD 553 1906) case of miliary follicular fibromas; Reitmann (AfDuS 93 417 1908) Neumann (DWchn 101 1263 1935) Dalton (ADS 44 899 1941) Crossland (ADS 67 122, 1953)

Hypoparathyroidism.—The skin changes in hypocalcemia were studied by Simpson (BJD 66 1 1954) whose cases included idiopathic hypoparathyroidism post thyroidectomy hypoparathyroidism, parathyroid adenoma steatorrhea and celiac disease and whose review of the literature was informative The main types of skin changes seen in hypoparathyroidism are (1) alopecia transverse grooving of nails, and edema (2) dry scaly pigmented skin, scanty hair growth and brittle nails; and (3) secondary onychomycosis.

Dry, rough, puffy scaly skin manifestations were noted by Cantarow (APediat 49: 293, 1932) Pigmentation is common in idiopathic hypoparathyroidism, less so in steatorrhea (Foerster: JCutD 34: 1 1916 Cantarow) Dermographia and localized areas of puffiness o frank edema ha e been reported, usually limited to the face o dorsa of the hands and feet (Levy: MedClinNoAm 31: 243, 194) A vesicular eruption developing into marginated, solid, purplish red patches of flaky dermatitis was seen by Learner and Brown (JClinEndocrin 1 3: 761 1943) and cheilitis and glossitis were also present. Impetigo herpetiformis (q.v) has been related to hypocalcemia see Ferriman (ProcRoySocM 46: 303, 1933) Seborrheic dermatitis has been related to steatorrhea (Cooke Modern Trends in Gastro-



Figs 933 and 934.—Lichen myxedematosus, showing knee and popliteal regions of Dr John H. Dalton patient.

Enterology Butterworth, 193_) Brittle grooved nails and sometimes moniliasis of the nails, were noted by Simpson, and alopecia was seen in almost all cases following attacks of tetany The hair is generally thin, lusterless and brittle and may be patchy and scant.

All in all, the changes resemble those of hypothyroidism, and the end effects of several deficiency conditions re somewhat alik being suggestive of decreased growth and accelerated aging

Pregnancy—Symptomatic eruptions in pregnancy were reviewed by Costello (NYSJM 41 849 1941) who listed the etiologic factors as endocrine, toxic and neurogenic. Urticaria dermographia generalized pruritus, pruritus vulvae prurigo herpes gestationis, impetigo gestationis, molluscum fibrosum gravidarum pigmentation, edema, hyperhidrosis, volar telangiectasis and hypertrichosis were noted. Herpes gestationis is probably dermatitis herpetiformis (q v) occurring in pregnancy See also Hypertrophy of the gums. Hirsutism has been known to develop during pregnancy; the hair fell out after parturition in the remarkable cases reported by Stoddard (AmJObGyn 49 417 1945) The appearance of vascular spiders and palmar erythema during pregnancy was studied by Bean et al. (SGO 88 739 1949) the blood vessels being affected by the chemical and hormonal alterations accompanying the condition. Moles and neurofibromas generally become larger and pig

mentation increases during pregnancy The administration of estrogenic hormone frequently increases skin pigmentation (Hamilton PSExperBiol 40 502 1939)

Pruritus accompanying pregnancy may be extreme and exhausting to such a degree that termination of gestation may be considered (Stander in Williams Obstetrics, Appleton Century 1930 p 580) Itching may affect mainly the vulvar region, explicable perhaps by engorgement and stasis, monilia, or the patient s response to her extremely high estrogen level. Pruritus was thought probably to be of toxic origin, and its rebelliousness to treatment was remarked upon by Rostenberg (UCutRev 40 269 1936) see Costello (ADS 43 192 1941) It is generally worse at night worse in summer months, and worse toward the end of pregnancy (DeLee and Greenhill Principles and Practice of Obstetrics Saunders, 1943) Palliation may be obtained with cool aluminum acetate baths antihistaminic drugs, injections of vitamin B complex, oral administration of methionine (Gainey pers. comm., 1951) and high protein diet. Cortisone and ACTH if adequately dosed, sometimes work well.





Fig 935.—Dermatitis dysmenorrheica. Rash appeared regularly 3 or 4 days prior to menses (Urbach InternatClin 2 161 1939)
Fig 936.—Dysmenorrheal eruption. (Dr Fred Wise)

Erythema multiforme, with urticarial and annular lesions is sometimes seen (Davis BJD 53 143 1941) Such cases are dramatically helped by cortisone. In a survey of Boston Lying In material, comprising 50 000 deliveries Crawford and Leeper (ADS 61 753 1950) found 11 cases of herpes gestationis, a variety of coincidental dermatoses, and numerous examples of dermatitis medicamentosa toxic erythemas, pruritus, prurigo and urticaria. Contact dermatitis seen in pregnancy sometimes is due to excessive use of soap at that time or to lubricant oils used by the patient for massage

Pregnancy often has beneficial effects on the skin, noted Hollander and Vogel (PaMJ 48 454 1945) Acne may disappear and superfluous hair may diminish. Psoriasis has been known to disappear reappearing after childbirth.

Skin tests for the diagnosis of pregnancy have been devised. A gonadotropic hormone was injected intradermally by Pollatschek and Porges (J 93: 559 1929) and antuitrin S was

the test material tried by Gilfillen and Gregg (AmJObGyn 32: 498, 1936) to which 24 of 76 males tested by Weisman and Yerbury (Mileo 145: 203, 1937) reacted positively. This test was adjudged worthless by Gill and Hoskins (BMJ 2: 1069 1937; see p. 1199). Placental tissue was the antigen used by Grumkin (AmJSurg 31: 59 1936), but this too is unreliable, according to Graffagnino and Hamm (SouthMJ 31: 169, 1938). Diluted colostrum was tried by Falls et al. (AmJObGyn 41: 431, 1941) with interesting results somewhat difficult to interpret, but Goldman et al. (J 119: 130 194_) reported this test correct in only 70% of the cases.

A skin test for recognizing eclampsia early was undertaken by Belikoff and Manevitch (abs BMJ 2: 899 1938) using the serum of an eclamptic patient as antigen.

Gynecomastia, unexplained, has been observed to make its appearance in the course of various extensive dermatitides, including mycosis fungoides, atopic dermatitis, autoeczematization and psoriatic exfoliative dermatitis (Wheeler et al.: ADS 68 685 1953). Enlargement of the breasts occurs in young men given estrogen e substances fo acne if overdosed, but it eventually disappears after withdrawal of the hormone.

Dermatitis Dysmenorrheica is a peculiar dermatosis which occurs rarely in women having dysmenorrhea, manifesting itself during the menstrual periods and at no oth r time. The eruptions consist of usually symmetric lesions affecting the face trunk, and extremities, appearing in the form of erythematous patches, urticarial wheals, or more often, vesicula eruptions resembling eczematous dermatitis (Urbach InternatClin 2 1939). Blood serum obtained during an urticarial flare and readministered to the patient in the intermenstruum caused reappearance of urticaria but did not affect controls (Harri

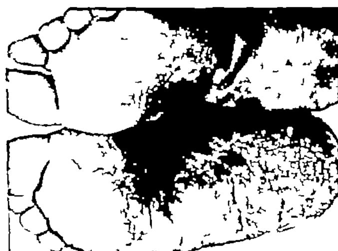


Fig 117 —Keratoderma climactericum (Haxthausen) (Dr O G Costa.)

son J 100 738, 1933). Not all e) lic rashes of menstrual periodicity are dyshormonal. Repair of cervical erosions, endometritis or cystitis due to cystocele may rid a woman of focal i fection nd dermatitis secondary thereto. Yet some cases of recurre nd of acn respond t e to suitable doses of estrogen and to no other medical ffort.

See also Menstrual purpura, Recurrent herpes, and Keratoderma climactericum; Sangar (MW R 11 1273, 1937) angioneurotic edema Donald (BMJ 1 899 1937) edema at time f periods relieved by estrogen administration; Scholtz (DeutMWchn 67: 842, 1941)

Keratoderma Climactericum was the title given by Haxthausen (BJD 46 161 1934) to a usually asymptomatic affection characterized by the occurrence of circumscribed hyperkeratoses of the palms and soles of obese and hyper plethic women at the menopause who may have arthritic symptoms also. Hypothyroidism underlies the development of volar hyperkeratosis in certain instances (Cervino et al. Endocrinol 22: 615 1938). Goldberg (ADS 40 67 1939) cured his case by injections of 2,000 units of estrogen in oil twice a week. Lynch (ADS 48: 270 1943) described the commencement of the disturbance with sharply circumscribed oval papules which progress, become scaly and eventually coalesce after which fissures may appear and secondary infection may develop. His histologic studies revealed mainly hyperkeratosis with some swelling and degeneration of elastic and collagenous tissues and mild lymphocytic inflammation. The patients of Garbe (ADS 49 254, 1944) responded well to estrogen but relapsed when it was discontinued. Volar

hyperkeratosis in circumscribed areas with itching sometimes, and fissuring if severe affects palms as well as soles. The lesions are fluorescent under Wood's light, and may respond to corrections of nutrition, high protein diet and injections of vitamins as well as to balancing the hormonal status of the patient. See Dermatitis of the hands (p 879)

Males with disease of the volar skin closely resembling what is described as keratoderma climactericum occasionally appear in my practice and prove responsive to estrogenic hormone therapy

Male Castrates.—Skin changes described in these individuals include a pasty sallow gray coloring with a lack of normal pinkness. On testosterone therapy flushing of the skin, increase of oiliness, increased growth of hair and increased pigmentation of exposed areas were noted by Hamilton and Hubert (Sci 88 481 1938). They observed a patient who sunburned easily and who, 5 months after sun exposure was given testosterone; he then developed pigmentation of the previously exposed parts. Carotene is increased and melanin reduced in the skin of the castrate and this situation reverses when testosterone is given, according to Edward et al. (Endocrinol 28 119 1941)

GOUT

Gout is characterized by the deposition of urates, chiefly the biurate of sodium in and about the tissues of joints, particularly the cartilages, most frequently affecting the metatarsophalangeal joint of the great toe the knee



Fig 938 —Gouty tophi helix of ear (*Dr Jonathan Meakins*)

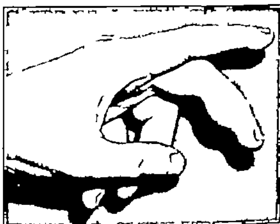


Fig. 939 —Gouty tophus of finger (Dr Jonathan Meakins)

joint and joints of the fingers. Urates are deposited also in the soft tissues of the joints, and in the eyelids the cartilage of the ear and the subcutaneous tissues, especially of the hands. Tophi are nodules of considerable size and over them the skin may ulcerate so that there occurs discharge of hard chalk like masses followed by temporary healing. Urates do not obstruct the x rays more than soft tissues do. The blood plasma uric acid exceeds 6 mg /100 cc in 96% of the cases (Talbott Gout Oxford Univ Press, 1945)

Observations suggesting the diagnosis of gout include: precipitation of attacks by relatively trivial trauma, attack following holiday dietary indiscretion, arthritis occurring within the first 6 postoperative days, precipitation of attack in gout-susceptible person by liver therapy, ketogenic diet, administration of Salyrgan or other diuretics, ergot or insulin, rarely (Rutledge and Bedard PSMMC 1 149 1937). In polycythemia or leukemia a patient is prone to acquire gout. Some 95% of gouty persons are males, and the first attack generally occurs after age 35, gouty arthritis being the common form of acute arthritis affecting men of 40 or over. Attacks are most frequent in the spring and fall, but may occur in any month. Attacks are prone to appear between ... A.M and in no other form of arthritis does the disability develop so rapidly. The pain is usually extremely severe. Only a few joints are involved, as a rule, the great toe most commonly with maximum tenderness over the mesial aspect of the metatarsophalangeal joint. The affected foot is not cold and bluish white, but is warm and flushed, the skin often shiny showing edema and later desqua

mation. Attacks are brief lasting from 7 to 21 days, and there is a tendency to full restitution of articular function between attacks. Olecranon bursitis is common in gout, and renal colic or nephritis often develops.

Volar erythema with hyperkeratosis at pressure points, itching and burning with or without painful fissures may improve on antigout therapy (Barber: ProcRoySocM 31: 01 1938). A man with urticarial and crusted papular lesions had a high blood uric acid concentration and was relieved by low purine diet, reported Cumel (DZtschr 78 73 1949).

Exacerbations are preventable by adherence to a low purine diet (Hench J 116: 453, 1941) which allows milk eggs, cheese, caviar shad roe nuts, gelatin, sugar sweets tea, coffee cocoa, fats of all kinds fruits of all kinds, cereals except whole grains, bread except whole grains, vegetable soup without meat, and vegetables of all kinds *except* lentils, spinach, mushrooms, peas lima beans, navy beans, kidney beans, kohlrabi asparagus and onions. Foods rich in purines include sweet breads, liver kidney squab, tongue turkey pork, veal, sausage beef goose anchovies, sardines trout, pike perch codfish, lentils, gravies, meat extractives and meat soups. All wines and liquors should be avoided.

The intermittent use of cinchophen has usually been necessary. A method of dosage recommended by Graham (ProcRoySocM 31: 1 1937) is 0.5 Gm. t.i.d. for 3 or 4 consecutive days each week for several weeks. During the taking of cinchophen, the patient should ingest also a quart or more of water a day and maintain alkalinity of the urine with sodium bicarbonate 2 teaspoonfuls in the morning and one in the evening. Early signs of intolerance of cinchophen are nausea hives or other skin reactions and urobilinogenuria. On the appearance of such symptoms, the drug *must be stopped*.

The prolonged administration of the urate diuretic drug probenecid (Benemid) effectively removes the urates that are deposited in the joints and bursae and recent studies in a limited number of cases have shown that its long term use reduces the size of established tophi, according to Smyth (J 15 1106, 1953) who noted further that spectacular results indicate that phenylbutazone (Butazolidin) may be a useful drug in both the acute and chronic stages of this disease. Benemid therapy is only rarely ineffectual, but in an individually adjusted dose of 0.5 to 3.0 Gm. daily, it produces a drop in the serum uric acid to normal within 3 to 6 weeks in patients on high fluid intake whose urines are kept alkaline (Bartels: AnnIntM 4. 1 1955). Attacks of gout may continue for several months after treatment commences, but in several patients these attacks were not preventable by colchicine either (Bartels: AnnIntM 4.: 10, 1955).

Surgical removal of tophi relieves pain (Linton and Talbott AnnSurg 117: 161 1943).

ACTH or cortisone will effect rapid relief of an attack (Friedlander J 145 11 1951); their administration reduces blood uric acid levels in both normal and gouty subjects (Cost et al.: AnnMed 53: 64 1953).

AMYLOIDOSIS

The skin, as well as internal organs, may be the site of deposits of amyloid a homogeneous degenerative substance which iodine stains a mahogany brown and which characteristically is deposited about the endothelium of capillaries. Cases can be grouped (Michelson and Lynch ADS 32 363 1935) as (1) localized amyloidosis cutis (2) generalized amyloidosis with cutaneous involvement (3) systematized amyloidosis with skin lesions. The classification preferred by Goltz (Med 31 381 1952) segregated 4 groups of cases primary systemic secondary or parenchymatous; localized forms and amyloidosis secondary to multiple myeloma. In primary amyloidosis, amyloid is deposited throughout the body blood vessels, connective tissues and muscles bearing the brunt of the disease the parenchyma of organs being largely spared. Almost half of these patients have cutaneous and mucosal lesions and macroglossia. Purpura is the commonest skin lesion. In addition to cutaneous infiltrations, other changes include ulceration, alopecia and nail involvement simulating onychomycosis.

Localized Amyloidosis may be primary or secondary. The eruption which may be called lichen amyloidosis, is generally composed of firm seemingly translucent, hemispherical papules, smooth and shiny or slightly scaling brownish or dark brown or yellowish or livid in color grouped in patches but tending to remain discrete intensely pruriginous, and situated most commonly on the extensor surfaces of the extremities, especially the legs, the flexor surfaces of joints being almost invariably free. From the basic papules evolve 3 common forms (Palitz and Peck ADS 65 451 1952) discrete papular lesions lesions resembling hypertrophic lichen planus and aggregations of papules extending so as to simulate lichen chronicus simplex.

In a study of the occurrence of amyloid deposits in the skin, Freudenthal (AfDuS 162: 40 1930) found them present in 16 of 50 specimens of keratoma, in 40 of 500 epitheliomas examined, in lesions scattered over the body and in the normal-appearing skin of 8 patients with lichen amyloidosis, in 8 of 10 cylindromas from the face and in unique cases which respectively resembled mild facial erysipelas, redness and swelling of the face, an epithelioma like lesion of the face and a curious livid nodule on the cheek. He found in rare instances intra-epitheliomatous inclusions of amyloid, and amyloid clumps between the epithelial cells of the epidermis.

Lumpy lesions of the chest and face resembling keloid were observed in the astonishing case of Bizzozero and Midana (AnndeD 10 18 1930) A similar curious tumor developing on a woman's nose was reported by Holtzman and Skeer (ADS 67: 187 1953)

Dostrovsky and Sagher (ADS 44: 891 1941) reviewed 5 localized cases, utilizing in diagnosis the intradermal injection of 0.1 cc. of 1% Congo red solution, which stains amyloid nodules red.

Treatment is unavailing but when amyloid bearing skin was moved by surgical flaps to an amyloid free location no more amyloid formed but that which was there remained (Sagher ADS 53 342 1946)



Figs. 940 and 941.—Primary systematized amyloidosis with macroglossia. (Wells DJD 44 149 1952.)

Generalized Amyloidosis presents no characteristic eruption. The parenchymatous organs are involved chiefly the skin little. Sore tongue is a typical and extremely distressing feature. In generalized cases the diagnosis depends upon the Congo red test, which is the most important diagnostic criterion and on the presence of enlargement of the spleen and liver and the hypoproteinemic syndrome (proteinuria diminished blood protein, hypercholesteremia and anasarca) purpura occurs uncommonly (Moschcowitz AnnIntM 10 73 1936) Kidney failure due to amyloidosis is a common cause of death in leprosy

The Congo red test (Bennhold AfKlinM 143: 33, 1923; Nomland: ADS 33: 85, 1936) is performed by injecting intravenously 10 to 15 cc. of 1% solution of the dye and withdrawing blood samples after 4 minutes and again after 1 hour the first sample being the measure of 100% Retention of 90% or more is required for the test to be read significantly positive (Harmon et al. AIntM 70: 416 1942)

Systematized Amyloidosis designates the group of cases which present (1) little involvement of organs usually affected in generalized amyloidosis, (2) involvement of organs ordinarily spared in the commoner form (3) papular or nodular skin lesions due to deep-seated amyloid deposits (4) deposits that do not react in the ordinary manner to the usual stains, (5) absence of





Fig 942.—Localized amyloidosis. (Division of Dermatology Department of Medicine University of Chicago, from Wiener Skin Manifestations of Internal Disorders, Mosby 1947.)

Fig 943.—Amyloidosis cutis. (Dr H. H. Kittredge.)



Fig 944.—Lichen amyloidosis, histology Methyl violet stain shows sharply circumscribed amyloid nodule in superficial cutis. (Abramowitz and Isaak AD&S 40: 13, 1939.)

concurrent disease to account for amyloid change. Glossitis with macroglossia is usually an early and painful accompaniment, and changes in skeletal muscles give severe aching symptoms. Amyloid infiltrations of the lingual, esophageal, cardiac and skeletal muscles were major features of the 2 cases of Smith and Woodhouse (JPathBact 47 311 1938). Primary systematized amyloidosis is "a rare constitutional disease in which without apparent cause there is extensive deposition of amyloid throughout the body with a peculiar affinity for smooth and striated musculature and the skin," according to Brunsting and Macdonald (JID 8 145 1947).

In their 4 cases, the eruption consisted of yellowish-brown pigmentation of palpebral, mandibular and submental areas, and small, shiny, amber-colored papules on the forehead, eyelids, face, neck, hand, trunk and oral and lingual mucosae. Pinhead to dime size subepithelial ecchymoses appeared at the site of the eruption. Macroglossia with impairment of speech and swallowing, muscular pains, dyspnea, weakness and gastrointestinal dysfunction were the features and interestingly Bence Jones proteinuria was found in 3 of the 4 cases, along with sternal marrow changes suggestive of myeloma. Atkinson (MP&Circ 195 31, 1937) had reported amyloidosis in 40 of 643 collected cases of multiple myeloma and Bence Jones protein was present in 10 of the 40. The nature of this coincidence is not understood.

The course is, as a rule, progressively downward. Evidence that amyloid may sometimes resolve at least partially was adduced by Reimann (J 104 1070 1935) from the fact that results of the Congo red test improved in his tuberculous patient. Rosenblatt (AIntM 57 562, 1936) too has seen improvement.

Etiology and Pathology.—In general amyloidosis the brunt of the disease is borne by the parenchymatous organs. Chronic suppuration, as in empyema, osteomyelitis or cavitating tuberculosis, is generally the causative factor. Hyperglobulinemia produced by injections of sodium caseinate into rabbits was followed by the development of amyloidosis, reported Eklund and Reimann (APath 1[illegible] 1936). Jaffé (APath 1[illegible], 1936) was able to alter collagenous tissue into amyloid-like tissue by inducing hypersensitivity to abnormal proteins. Amyloid appears in the guinea pig in association with chronic scurvy (Pirani et al.: Sci 110 145 1949). Association with varicosities suggested the role of stasis in the development of primary localized amyloidosis of the legs, thought Wolf (ADS 67 407 1953).

The structureless or slightly granular amyloid substance is found in greater or lesser quantity about the capillaries of the dermis and dermal papillae lying beneath the epidermis and separated from it by a thin layer of connective tissue; also about the cutaneous appendages in the deeper layers, and in masses that may even enclose fat cells. *Its presence calls forth no inflammatory or foreign body reaction.* The specific histologic technic for demonstration of amyloid was described by Pinkus (ADS 65: 304 1932), who left his paraffin sections in gentian violet solution for a few hours, dried, dissolved out paraffin and mounted in balsam. Giemsa's stain alone stains amyloid light blue while ordinary hyaline stains pink.

See Philpott and Freshman (ADS 33 976, 1936): lichenoid case in tuberculous man. Rosenblum and Kirshbaum (J 106 [illegible] 1936): case in multiple myeloma. Binkley (ADS 3[illegible] 110 1938): macroglossia in old woman. Hulison (ADS 40 1024, 1939): legs involved in old man. Spiegel (ADS 45 623, 1942; 48 112, 1943): yellow plaques on a woman's cheeks. Hass et al. (APath 35 [illegible], 1943): systematized amyloidosis in plasma cell myeloma. Lindsay and Knorp (APath 39 315 1945): systematized, with nasal obstruction and hemorrhages. Golden (AIM [illegible] 417 1946): systematized, with glossitis. Greenbaum and Bauer (ADS 68 [illegible] 1943): primary lichenoid [illegible] topy. Weil (JID 84 [illegible] 1953): systematized case, woman with macroglossia. Dinnigan (J 149 148, 1952): glossitis in systemic amyloidosis.

HEMOCHROMATOSIS

Hemochromatosis (hemosiderosis, bronze diabetes) is a rare disease characterized by the deposition of large amounts of hemosiderin in glandular tissues and hemofuscin in the connective tissues, spleen and smooth muscles (Sheldon: Hemochromatosis, Oxford University Press, 1935). The onset is usually after the age of 35 years. Pigmentation and cirrhosis of the liver and pancreas with impotence, diabetes, ascites and terminal jaundice are the typical features. Pedigree studies suggest that this inborn metabolic error is transmitted through the female (Lawrence: Lancet 2 1055, 1935; 1 736, 1949). Iron is increased in quantity in all the tissues except the blood, brain and colon, and there may be relatively enormous amounts in the liver, pancreas, lymph nodes, thyroid, pituitary, salivary glands, choroid plexus and heart. Butt and Wilde (APath 26: 262, 1938) observed that of 30 known cases, 29 were males. The bronze skin is of a hue between that of Addison's disease and that of argyria.

The slow progressive course of the disease was remarked by Althausen et al. (AIM 88: 553 1951) who thought it probably begins early in life. The immense absorption of iron from the intestinal tract is unexplained (Fischer: ADS 66 [illegible] 195[illegible]).

Exogenous hemochromatosis occurs in patients who receive unusual quantities of iron or of blood by transfusion. 13 such cases ha l g been collected from the literature and 1 reported by Norris and McEwen (J 143: 740 1950)

Th skin biopsy usually shows iron-containing pigment in the propria of the sw at glands and superficial capillaries of the cutis. The intracutaneous injection of 0.5% potassium ferrocya ide in 0 01 normal HCl yi lds a blue colo diagnostic of the presence of iron (Fishback: JLabClinM _3 93 1930) Cases in which skin pigmentation was lacki g were described by John (J 11*: 227_, 1930) and Cantarow and Bucher (AIntM 37 333 1941) Pigment is absent in 16% of the cases, stated Magnuson and Raulston (AnnI tM 16; 687 194) reporting their spectrographic st dies. Needle biopsy of the live may aid in diagnosing such patients (Topp and Lindert: Gastroenterol 10 813 1948)

Asthenia is a frequent complaint. Regressio of secondary sex characters is a symptom with pallor and loss of axillary, pubic and beard hair (Kepler et al.: AnnIntM 14: 810, 1940) The color changes in the skin are not invariably present and may appear early o lat in the course of the disease. Differentiation from Addison's disease and from argy is is readily made by noting the changes in the urine. The cirrhotic liver is smooth and firm but not very hard. The patient does fairly well if the diabetes is controlled, but in the late tages this is difficult to do. A high-protein high-carbohydrate diet l recommended (Bloom: VaMMonth 66: 70 1939) Bleeding is a successful means f r depleting the depots of iron (Davi nd Arrowsmith: AnnIntM 39: 723, 1953; Davey et al.: BMJ 1511 1954) Diabetes was absent in 15 of the 27 cases of Stauffer et al. (Gastroenterol *7: 31 1954) Iro torage diseases we e classified in the valuable essay of Kleckner et al. (J 157 1471 1955)



Fig. 248.—Ochronosis mottled pigmentation of f ce, and spots on conjuncti ae, in the dermis, masses of pigment of bizarre shape (Laymon ADS 67 533, 1953)

OCHRONOSIS

Ochronos the nam suggested by Virchow (ArpathAn t 3": 1_, 1866) for rare disorde charact rized b grayish, brownish, or blackish pigme tation of the cartilages, ligaments, t d ns a d intima of the large blood vessels. I addition to the deposits I the i ternal structures the pigment is freque tly found i the sclera ep dermis nd occasionally the nails. The cartilages of th ears nd nose have a peculiar bluish ti t. The bla ked appearance a of newly shined boots i due t a melanin type of pigment in the cartilage ot th perichondrium. There may be dark pigmented spots i the sclera a d sk (Oseabora J 110 576, 1938; Sm th: J 120: 1282, 1942)

According to Laymon (ADS 63: 796 1951; 67 533, 1953) the urine in ochronosis may be rmal in color whe freshly v ided but graduall turns color on exposure t ai because f the polymerization of homogentisi cid to a bl ck, insoluble pigme t f high mo l w weight The color hange is rapid i the presence of alkali hence the name alkapton ria. La mon quoted Fitzpatri k d Lerne regarding th perti ent metabolism f tyrosine: i the thyroid gland it is iodinated to form thyroxin ultimately in the drenal medulla, it con rted into epinephrine a d nor-epi ephrine; and i the pigment cells, it is co erted i to m la in. I addit on tyrosine undergoes changes that convert it i t homogentisic acid, whi h, if properl metabolized, would be degraded ulti m tely to carbon d oxide nd w ter I alkapton ria such degradation does not occur, and the compound ccum lates in xtracellular fl ids, where it oxidizes into the da k, i sol ble product which h racteri es ochronosis. Why it selectively localizes i cartilage is u known. Th accumulation is pparently d t the absence of one or more enzymes which ormally l ri g bout the degradation of homoge tisic acid. This bsence is hereditary usu lly as a recessive rarely a dominant, Mend lian ge etic character

Cortisone was clinically beneficial in the patient of Cope and Kassander (J 150: 997, 1953), for during periods when it was not given there were recurrences of joint pains, and reducing substances reappeared in the urine.

CALCIFICATION IN THE SKIN (CALCINOSIS)

True osteoma (q v) has been observed in the skin. Calcification occurs locally too in arteriosclerotic patches caseous tuberculous nodules, laparotomy scars (rarely) chronic inflammatory lesions, fat necrosis secondarily vascular thromboses scleroderma dermatomyositis, and some new growths, such as atheroma dermoid cyst basal cell carcinoma nevus calcifying epithelioma fibroma, sarcoma and pseudoxanthoma elasticum (Epstein et al. ADS 28 510 1933 Maloney and Bloom ADS 23 245 1931)

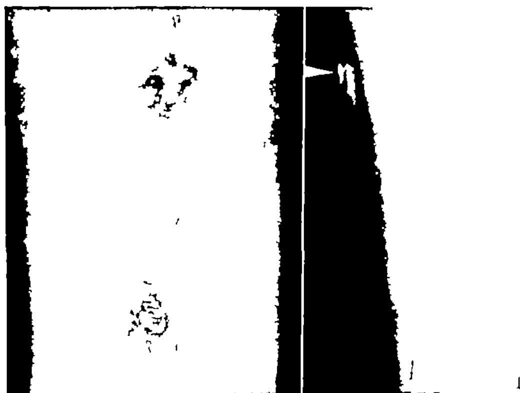


Fig 946.—Calcification in scars of an old man's leg.

Local Calcium Deposits in scars generally ha e followed severe blunt force but sometimes develop in clean wounds (Lewis SurgClinNoAm 1 1119, 1917; Bouton: These Paris, 1923) Masses of calcification occurred in the tissues of chronic eczema of the legs in an old man seen by Rachold (DWehn 99: 1141 1934); about a varicose ulcer observed by Wendlberger (DWehn 102 50 1936); in an old leg ulcer reported by Sencar (ADS 38 ?67 1938); in the crusted, gran lomatous scar of an ancient burn on the chest (Paco ADS 64: 622 1946) and in a gluteal lump that followed injections of mercury (Lowenfish: ADS 54 457 1946; see ADS 31: 715, 1935) Weber (BJD 45: 614 1936) noted calcific nodes in the subcutaneous tissues of the forearms and skin of a patient with cutis hyperelastica. Calcification in amputated legs from patients with diabetes mellitus was reported as not infrequent by Davis and Warren (APath 16 852, 1933) Postphlebitic dissemin ted cutaneous calcifications were found by x ray in ?0 women in 1 year by Lindner (AfDuS 196 403 1953) when he looked fo them systematically I ha e seen calcification in the lesions of a scleroderma like linea nevus of the arm.

Formation of cartilage nd bone in an old cystotomy wound was reported by Chauvin and Roulacroix (Jd'Urol 27 465 1929) Calcinosis and bone f rmation in a plaque of morphea comprised an unusual breast tumor described by Ro chese (AmJSurg 39 635 1938) The basis of bone formation is always pathologically altered tissue (Musger: ActaD-V 16 1 1935)

Solitary Congenital, Calcific Nodules.—Winer (ADS 66: 204, 195_) reported 3 cases, affecting the fingers, foot and knee of young children, giving histologic fi dings.

Calculi are found occasionally in the umbilicus and beneath the prepuce. Thomas (UCutRev 41: 318, 1936) listed 3 types of preputial calculi: smegma concretions, composed of cells, lipid matter bacteria and lime; concretions composed mainly of phosphate from urine retained in the preputial sac; and migratory stones, i.e., those formed elsewhere. The case of Ingraham (J 106: 106, 1935) was preputial.

Metastatic Calcification.—The lungs, stomach and kidneys are the main sites of deposition of calcium as a result of excessive absorption from the normal depots (Weidman and Shaffer: ADS 14: 503 1926) This may occur in leukemia, metastatic new growths, hyperparathyroidism and osteomyelitis, and is associated with hypercalcemia (Maloney and Bloom: ADS 23: 745 1931; Grayzel and Lederer: AIntM 64: 136, 1939) It is a hazard of vitamin D overdosage (q.v.) and has followed excessive intake of milk and alkali in patients with peptic ulcer (Dworetzky: J 155: 830, 1934) A primary disease is preliminary to soft tissue calcification, which is a secondary condition in almost every instance stated Wheeler et al. (AnnIntM 36: 1050 1953) In their 66 cases of calcification of various causation, the primary diagnosis was oftenest scleroderma, Raynaud's syndrome or dermatomyositis. When calcification is found, one must also conside the possibility of rheumatoid arthritis acrodermatitis chronica atrophicans, hyperparathyroidism, vitamin D intoxication metastatic bone disease multiple myeloma, Paget's disease of th bone, renal failure a d pseudohypoparathyroidism.

Lipocalcinogranulomatosis.—Symmetric tumors over the scapulae and elbows firm and painless, gradually i creasing in size, have been seen in children. Excision and microscopic examination showed deposits of cholesterol and calcium, decomposition of tumors to form cavities filled with necrotic m terial, and the formation of granulation tissue about these. The disease m y be a cholesterinic lipoidosis. See A dreas (abs J 141: 1126 1949)

Metabolic Calcinosis is manifested by abnormal deposition of calcium salts in the skin, subcutaneous tissues and superficial fascia in plaques and nodules of 1 to 4 mm. diameter, usually affecting the extremities and tendon insertions, occasionally with perforation and discharge through the skin, at times associated with scleroderma, but not associated with excess of calcium in blood or urine (Graham: ADS 41 864 1940) Calcinosis falls into 2 main classes: (1) *calcinosis universalis* the general, diffuse, or metabolic form, and (2) *calcinosis circumscripta* a more localized form, of which many cases have been described under the title of hypodermolithiasis, or chalk gout (Rosenberg J 115: 1791 1940)

Calcinosis Universalis.—Tumors or plaques, from pea to walnut size appear under or in the skin, involving the region of larger joints and even the back. The overlying integument becomes red and adherent perforation occurs, with the discharge of creamy oleaginous, gritty material the indolent, sluggish ulceration heals with scarring and the involvement leads to contractures, inanition and eventually in many cases, to death. The wrists, knees, elbows and hips are the most usual sites. The course extends over a period of years. Atrophy of the musculature and stiffness of the joints interfere gravely with the patient's way of life, and the gradual downhill course of the patient is pitiable (Salvesen and Böe ActaMScand 92 389 1937)

Calcinosis Circumscripta.—This type involves the upper extremities, especially the hands and elbows. Swelling of the phalanges occurs and calcareous nodules develop These may rupture and discharge. There is some interrelationship with nodular xanthoma, which affects the same locations and in the lipid of which calcium may be deposited and with Raynaud's disease and sclerodactylia, which are perhaps associated with dysparathyroidism.

Etiology and Pathology.—Patients ha ra ged in age from a few months to senility There is no predilection as to sex. Roentgenologic exami tion reveals typical subcutaneous deposits of opaque subst nce (rates do not obstruct the rays) Chemical analysi of the minerals shows them t be composed of calcium phosphate and ca bonate the phosphate predominating in approximat ly the proportions found in normal bone On pathologic examination the calcification seen t involve swollen and retrogressively changed fibrous tissue. The blood calcium d phosphorus level re ge erally normal (Durham AIntM 42: 467 1928) Robinson (BiochemJ 17: 286, 1923) believed that phosphatase enzyme plays an important part; cting on phosphoric acid est r it liberates phosphoric cid, which atta hes calcium t itself According to Klotz (JExperM 7: 633 1905) calcification depends upon the intervening formation f soaps. Examining the mineral deposits by means of x ray diffraction methods in circumscribed and 1 generalized case, Cornbleet et al. (JID 12 171 1949) found them t have assumed the apatite patt rn. Hueper (APath 3 14 1927) produced metastatic calcinosis in dogs by means f the dministration f parathyroid extract. I terpret calcinosis as bei g closely related to xanthoma, f r if the lesion of xanthoma u dergoes calcification, the pict re would be that of calcinosis.

Treatment.—Excision of osteomas and of localized calcium deposits is satisfactory In universal calcinosis, Craig and Lyall (BJChildDis 28 29 1931) recorded benefit with sodium acid phosphate ʒiss daily and Kennedy with a ketogenic diet Three cases in children improved on this regime, to which Weber (BJD 47 400, 1935) added the administration of syrup of iodide of iron. Epstein et al. (ADS 21 510 1933) found ineffectual the usual low



Fig. 947.—Calcinosis universalis, lesions of elbow



Fig. 948.—Calcinosis universalis (Epstein ADS 34 267 1936.)



Fig. 949.—Calcification in calcinosis (Dr Fred Weidman.)

calcium low vitamin diet with the disodium phosphate acidifier they advised symptomatic treatment with incision and drainage when needed and suggested the trial of hyperpyrexia I had striking success in one case first seen in 1935 with the subcutaneous administration of an active parathyroid extract given to tolerance on alternate days. Roentgen examinations proved that this treatment prolonged in my patient did not decalcify the skeleton. Sodium acid phosphate had been given to this patient continuously Adhesive

tape applied to the plaques prevented their ulceration. Parathormone relieved her incapacity so that she was able to resume work as a librarian, which she did for 10 years, but died in 1946 with carcinoma of the ovary. Parathyroid extract was adjudged valueless by Comroe et al (AmJRoentg 41 749 1939) who recommended a diet low in calcium and vitamin D. Estrogen produced improvement, according to a report by Fleck (DWchn 126 993 1952)

See Durham (AIntM 42 467, 1928), review; Steinitz (ErgebInnMedKinderh 39: 16, 1931) review; Thomson and Collip (PhysiolRev 12, 309 1932) parathyroid activity; Weissenbach et al (AnndeMéd 31 594 1933) review; Brookes (QuartJM 3: 293, 1934) review; Rudolph (JPediat 4 342, 1934) boy with dermatomyositis; Wilson (J 104 391, 1935), old woman, fingers involved, hypercholesteremic; Bénary et al (BuocfrancD 43: 1176, 1936) calcium deposits in thighs and forearms of old woman with leg ulcers and scleroderma; Epstein (ADS 34: 367 1936) 2 cases, universal; Rothstein and Welt (AmJDisChild 52 368, 1936) universal, 2 cases in children; Cleveland and Agnew (BMJ 2 13 1937) circumscribed, in digits of 13-year-old girl; Atkinson and Weber (BJD 50 267 1938) review; Reimers (Acta Mscand 100 57 1939) universal in 6-year-old girl cured with sodium citrat by mouth and calcium intravenously; Taylor et al (AIntM 63 236, 1939) calcium metabolism; Byrom and Michalover (AnnIntM 18 226, 1943) universal, no help from parathyroidectomy; Van Wagendonk (Sbe Sci New Supp 99 16, 1944) relief with heat-labile ketone from cream; QMN (J 142 379 1950) therapy; Schiff and Kern (ADS 48 672, 1943) metabolic type, fatal in newborn.

HYDROA VACCINIFORME, LIGHT SENSITIVITY DERMATOSES AND PORPHYRIA

Hydroa Vacciniforme (Hutchinson's Summer Eruption) is a recurrent vesicular dermatosis which occurs in the summertime, chiefly in young persons, usually involving only the uncovered skin. This rare affection appears in early life and gradually subsides following puberty. The lesions develop in crops and consist of pinhead to pea-sized vesicles, or small acuminate papules which later undergo vesiculation and are usually confined to the cheeks, nose, ears and backs of the hands. Symptoms of itching and burning are comparatively slight. The duration of an individual vesicle is from 3 to 7 days, after which the lesion, which often exhibits more or less umbilication, becomes inspissated, and a yellowish or reddish crust forms, soon drops off and leaves a sharply defined, pitlike cicatrix. By the development of new lesions an attack may be prolonged for several days, although the average exacerbation seldom extends over a fortnight. Scarring is sometimes extensive. Occasionally 2 cases occur in 1 family.

Hutchinson's Summer Prurigo (Prurigo Aestivale) is the title applicable to mild cases of hydroa in which recurrent eruptions of prurigo-like papules appear, their earliest manifestation being erythema and urticaria-like swelling. On the face there may be similarity to lupus erythematosus. Vesicles may be present but the eruption is variable, phases of sensitivity to sunshine alternating with apparently partial or temporary desensitization. Distinction between hydroa vacciniforme and prurigo aestivale is ambiguous.

Differential diagnosis was based by Pick (AfDuS 146 406, 1924) on the following criteria. Hydroa vacciniforme begins in early youth and shows predilection for males; colliquative vesicles are the primary lesions; it leaves scars, is characterized by itching and burning but is not excoriated; and hematoporphyrin is relatively frequently present. Prurigo aestivale begins at a later age than hydroa vacciniforme and shows predilection for females; itching urticaria-like papules are the primary lesions, the disease disappears in the winter; in it so pruritus prevails, lichenification from excoriation develops even extensively and no hematoporphyrin is demonstrated.

These criteria of Pick quoted and examined critically by Epstein (JID 8 187 194) are not valid, Epstein stated, because (1) about one-third of the cases of hydroa vacciniforme begin before the third year of life and about four-fifths before the fourteenth year. Prurigo aestivale does not start so frequently in childhood; but all 5 original cases of Hutchinson's which Pick recognized as prurigo aestivale started at ages ranging from 8 to 15 years; earlier ages of onset have been reported. (2) Predilection for males in hydroa vacciniforme is generally asserted, and this is true of familial cases, which, however, constitute only 10% of all cases, among which there is actually a preponderance of females, for in the review of Senear and Fink (ADS 7 145 1923) of more than 59 cases of hydroa vacciniforme females led, 2 to 1. (3) The primary lesion of hydroa vacciniforme is urticarial, not vesicular. Blisters do not appear in all cases. (4) Mild eruption of hydroa vacciniforme frequently heal without scars and scars are not rare in prurigo aestivale. (5) There is no proof that porphyrins play a causative role in the prurigo aestivale





Figs. 950 and 951.—Hydroa vacciniforme.

Fig. 952.—Hydroa aestivale. (Dr. George Miller MacKee.)

or hydroa vacciniforme but porphyrins have been demonstrated in some cases of both conditions. In summary typical cases of either condition present a clinical state easily recognized, but there is no single criterion which will allow a hard and fast differentiation.

Eczema Solare, a term introduced by Willan, comprises a heterogeneous group of dermatoses alike in that there occurs more or less acute dermatitis following exposure to the sun. Epstein (JID 5 187 1942) distinguished among these (1) cases combined with or closely related to urticaria photogenica, (2) cases of eczematoid dermatitis partially or temporarily simulating prurigo aestivale, (3) cases of solar dermatitis, vesicular but without urticaria or prurigo and (4) cases which morphologically and etiologically belong to contact dermatitis.

Three types of pathologic reactions to light were distinguished by Epstein (JID 5: 225, 1942): (1) *immediate urticarial reactions:* these never occur in normal persons and they start with erythema, usually accompanied by pruritus, which develops within a few minutes after irradiation begins, may comprise with small exposures merely ¼ to 1 hour of erythema only and may with larger doses comprise urticaria limited to the test site, or with adequate exposure, complete whealing which exceeds the test site by a few millimeters; (2) *pathologic sunburnlike reactions* these differ mainly quantitatively from normal ultraviolet reactions often occurring in patients of the prurigo aestivale group; and (3) *reactions productive of lesions characteristic of prurigo.* Such reactions Epstein summarized as follows: (A) irradiation of previously diseased skin may lead to local provocation of prurigo within a few hours, or to provocation of prurigo on other parts previously diseased but not irradiated, or to no prurigo eruption on parts previously not diseased; (B) irradiation of normal skin, previously not diseased, may lead to no eruption on irradiated parts, or to prurigo after 5 to 9 days, or to prurigo after * to 4 days, or to prurigo at sites previously diseased but not irradiated.

These 3 types of reaction seem to be independent of each other and to correspond essentially to the 3 clinical entities, urticaria photogenica, eczema solare, and prurigo aestivale. Combinations of the types may be postulated to exist in explanation of the variety of clinical manifestations. The 3 types of light sensitivity are not due to specific wavelengths, for each has been provoked by more than one spectral region.

The provocation of lesions of prurigo aestivale may involve more than specific absorption of certain wavelengths. Local provocation on previously normal skin was, in Epstein's experiments, always dependent on the provocation of erythema, without which no prurigo appeared. Intensity of eruption increased in direct proportion to the degree of erythema, which was not necessarily due to ultraviolet, for erythema from other radiation such as alpha rays, had the same result. That erythema is necessary is indicated further by instances were prurigo was provoked by radiation which normally does not produce erythema. Yellow red light produced erythema and prurigo in the case of Urbach and Konrad (Strahlenther 32: 193, 1929) Yellow and ultraviolet light and sunshine filtered through window glass provoked dermatitis in a woman of 40 whose sensitivity had existed for 4 years, reported Burckhardt (Dermatologica 86 249 1942) A patient of Porter (BJD 66 417, 1934) showed sensitivity extending from ultraviolet throughout the visible spectrum into the infrared.

PHOTOTOXIC REACTIVITY and PHOTOALLERGIC SENSITIVITY —These were distinguished by Epstein (JID 5: 289 1942) While the mechanisms are different, they are clinically frequently combined Phototoxicity means primary nonallergic photoreactivity applicable indiscriminately *to all individuals and varying quantitatively with the dose. Phototoxicity* satisfactorily explains sunburn and the primary sulfanilamide response (Sulzberger: Dermatologic Allergy, 1940) and plays a role in berloque dermatitis (see contact photosensitization. But urticaria photogenica is not an example of photodynamic action (Blum: Photodynamic Action and Diseases Caused by Light Reinhold, 1941) nor can prurigo aestivale be so explained. Epstein theorized that in photoallergic persons precursor substance or proantigen exists which is altered by light into an antigen. Certain individuals can produce antibodies to such an antigen during suitable incubation period. Such antibodies may be fixed or circulating In the sensitized individual proantigen plus light plus antibodies results in dermatitis. Once this has occurred, the reaction time of subsequent reactions is brief than the incubation time of the first reaction. Some cases prove to have circulating passively transferable antibodies and others do not. Antigen produced in the recipient's skin through the action of light must depend upon proantigen transmitted with the donor's serum. While prurigo aestivale may be presented as a photoallergic manifestation other factors in addition to light sensitivity and allergy may contribute to its pathogenesis.

POLYMORPHIC LIGHT-SENSITIVITY ERUPTIONS were classified by Lamb et al. (ADS 62: 1 1950) among (1) the types which are plaquelike, contact eczematous, papular and prurigo-like and erythematous; ( ) solar urticaria with reaction to wavelengths of less than 3700 A.U to wavelengths of from 4000 to 5000 A.U and nonconfluent urticarial reactions to heat of infra red wavelength of 7900 to 14,000 A.U; and (3) the rare types, hydroa vacciniforme with and without porphyrinuria and epidermolysis bullosa like cases with porphyrinuria. Some two thirds of all cases are of the plaquelike type many of the eczematous. Histologically are found nonspecific inflammation with edema and cellular infiltration about the

dilated blood vessels. Porphyrins were absent from their patients, who, however showed creatinuria and somewhat depressed excretion of 17-ketosteroids, which was ameliorated by giving testosterone or equine gonadotropin intended to stimulate endogenous androgen production.

Urticaria Photogenica is manifested by the appearance of wheals at sites which have been exposed to light such as have been studied by Duke under the designation of "physical allergy" (q.v.). While cases of solar urticaria are clinically similar Blum et al. (JID 7: 99, 109, 1946) distinguished (a) those due to ultraviolet wave lengths of 3130 to 3650 A.U. (less than 3700 A.U.) wherein passive transfer of the patient's serum induces photosensitivity of the same wavelength limits locally in the normal recipient's skin, from (b) those due to blue and violet wavelengths of 4000 to 5000 A.U., wherein passive transfer cannot be accomplished; the condition is of sudden onset, and habitually exposed areas are significantly less sensitive to light than the areas usually covered by clothing. In type (a) the patient is not only extremely sensitive to the wavelengths that produce sunburn in normal persons, but the sensitivity extends to longer wavelengths so that the patient, whose urticarial response is elicited by a much larger fraction of sunlight, may suffer even in winter from relatively short exposures and is susceptible to radiation through window glass which almost completely protects normal persons.

Successful passive transfer of solar urticaria (3130 A.U. type) was achieved by Beal (JID 11: 415, 1948); see Callaway (ADS 41: 889, 1940); Rajka (J Allergy 13: 327, 1942). The power of the donor serum to induce reactivity was enhanced by U.V. irradiation of the donor prior to withdrawing his blood. After irradiation of and reaction by the recipient skin, subsequent irradiation did not evoke a response unless more serum was injected. Passive transfers from 2 cases of urticaria photogenica were accomplished by Epstein (AnnAllergy 7: 443, 1949), 1 of whose patients manifested purpura.

Solar urticaria: 2 cases of the type caused by wavelengths less than 3700 A.U. were relieved by Pyribenzamine so that ultraviolet exposure did not elicit wheals (Rubin et al.: JID 8: 169, 1947). Urticaria solare (4200 to 4900 A.U.) was well controlled with Pyribenzamine, noted Kesten (ADS 64: 221, 1951). In a man whose sensitivity was to wave lengths less than 3700 A.U. passive transfer was unsuccessful and there was no response to antihistamine given by Anderson (BJD 63: 230, 1951). Two young girls were cured by small doses of estrogen according to Lamb et al. (ADS 57: 785, 1948).

Porphyria.—Three main types of porphyria were classified by Watson (Lancet 1: 539, 1951): congenital, acute and chronic.

Congenital.—In this type there are well marked skin manifestations in the form of chronic erythematous and bullous eruptions, with exacerbations in spring and summer simulating hydroa aestivale. It is inherited as a Mendelian recessive, is commoner in males and occurs pre- or post natally with marked photosensitivity. Nikolsky's sign may be positive suggesting a resemblance to epidermolysis bullosa congenita. Neurological and abdominal symptoms are extremely rare. This type is sometimes associated with hemolytic anemia. The urine is red at times, the bones and teeth are stained pink, and they all show a red fluorescence under near ultraviolet light.

Acute.—The acute type of porphyria has its onset later in life with intermittent episodes of acute abdominal pain and neurological or mental symptoms as the predominant features, rather than skin lesions or photosensitivity which are rare. It is inherited as a Mendelian dominant, commoner in females. The urine is red at times and fluoresces but there is no fluorescence or pink-staining of the bones and teeth. Porphobilinogen is characteristically present in all cases of acute porphyria.

Chronic (Porphyria Cutanea Tarda).—This type occurs in young adults and is an altogether milder syndrome. There may be cutaneous, gastro-intestinal and, occasionally, neurological symptoms. Bullous eruptions, accompanied by pigmentation, hypertrichosis and milia appear on exposed surfaces, often following exposure to sunlight or trauma. Menstrual disturbances are

frequently complained of, particularly amenorrhoea. The urine is red and fluorescent, and there may be slight pink-staining and fluorescence of the bones and teeth. Porphobilinogen, coproporphyrin and uroporphyrin are present in the urine in varying amounts. These people tend to be constipated by habit

Porphyria according to Brunsting and Mason (PSMMC 22: 489 1947) is that rare familial metabolic fault in which abnormal kinds and amounts of porphyrins, especially uroporphyrin, are excreted in the urine and feces. The disease may be asymptomatic for years or for life and the urine may or may not have an abnormal coloration. Surveys of families in which this inborn error of metabolism occurs may disclose the presence of uroporphyrin or colorless porphobilinogen in the urine of apparently normal persons. Little is known of the factors which may precipitate the manifest syndrome of porphyria or influence its course In certain cases, a damaging influence on the liver either by disease such as cirrhosis or by hepatotoxic drugs or poisons (alcohol, barbiturates, arsenic, lead) appears to contribute to the development of obvious symptoms.

CLINICAL AND LABORATORY FEATURES OF PORPHYRIA

(Brunsting: ADS 0 551 1954)

	ERYTHROPOIETIC PORPHYRIA	HEPATIC PORPHYRIA	
		Acute Intermittent	Cutanea Tarda
Synonyms	Congenital or photo-sensitive	Acute toxic or idiopathic	Chronic
Frequency	< 1%	±60- 0%	±30-40%
Age of onset	Childhood	2nd to 4th decade	4th to 6th decade
Signs and symptoms	Photosensitivity (mutilating); splenomegaly and hemolytic anemia, erythrodontia, hypertrichosis, melanosis	Abdominal colic; paresis; psychic disturbances; hypertension; oliguria; constipation; melanosis (?)	Photosensitivity, melanosis; hypertrichosis violaceous hue; sclerodermoid skin; hepatic dysfunction
Urine color	Red	Port wine or normal (darkens on standing)	Normal or dark, red occasionally
Porphobilinogen	Absent	Present	Absent
Zinc porphyrin	Absent	Present	Present
Uroporphyrin	Type I	Types I and III	Types I and III
Marrow porphyrin	Markedly increased	Normal	Normal
Liver porphyrin	Slightly increased	Markedly increased (precursor mainly)	Markedly increased (porphyrin, mainly)
Course	Improved by splenectomy	Aggravated by drugs, pregnancy	Aggravated by drugs, alcohol

Porphyria finds clinical expression in various forms: the acute type with intermittent episodes of serious gastrointestinal or nervous and mental symptoms the congenital type which may begin in earliest childhood with red urine, erythrodontia, a mutilating eruption of the light-exposed skin and sometimes visceral complications; and the chronic types, which may belong to one or the other of the preceding appearing usually in adults and with a clinical course that is mild as a rule.

Porphyrins possess the power to sensitize the skin to light, but the photodynamic mechanism of this process is obscure. Attempts to reproduce an eruption in the skin of porphyric individuals by exposing them to sun or to artificial light have been for the most part unsuccessful.

In acute porphyria pigmentation occurs, but other cutaneous reactions are infrequent. In congenital porphyria, the outstanding change is the reaction to light by exposed surfaces of the skin. Bullous eruptions occur in chronic porphyria as a result of exposure of the skin to light and to minor trauma with the production of lesions similar to those seen in epidermolysis bullosa. The latter condition represents a fault in the binding mechanism of the skin with a varied hereditary pattern, but no actual relationship between true epidermolysis bullosa and porphyria has been established.

Fig 953 —Chronic d rmatitis accompanying chronic li er disease and bnormal formation of porphyria in the intestine (U bach KlinWchn 17 304 1938.)

Fig 954 —Porphyria, d ring acute ttack, howing swelling and vesiculation which de eloped in less than 1 week. (Brunsting and M son ADS 60 66, 1949)



Fig. 955 —Porphyria, same case as hown in Fig 954 but photographed prior to height of the ttack, at a time when both old and new lesions were present. (Drs. Louis Brunsting and Harold L. Mason.)

Patients with porphyria in whom the cutaneous manifestations were the presenting symptoms were described by Brunsting and Mason (ADS 60: 66 1949 Two patients, examples of chronic porphyria, had a mild bullous reaction of the exposed skin and uroporphyria in the urine. Another an example of acute porphyria, had, in addition, a severe episode of abdominal colic accompanied by uroporphyria and porphobilinogen in th urine. In this case they discovered that the mother of the patient had latent porphyria. The 3 cases developed the disease in adult life following chronic hepatic dysfunction associated with alcoholism.

The changes which occu in the skin in chronic porphyria include melanosis, hypertrichosis, milia and a chemical and physical alteration of the connective tissue which renders the surface layers susceptible to trauma and gives rise to a blistering reaction to light. Only the exposed skin is so affected, presumably through the toxic influence of cumulative doses of light, although the blisters cannot well be reproduced by artificial means and cannot be reproduced at all on the skin that has been protected from light. These changes occur also in epidermolysis bullosa, which is likewise an inherited abnormality of the skin; b t the two conditions are entirely distinct. In epidermolysis bullosa, trauma alone is the precipitating agent, and the pressure surfaces such as the palms and soles are primarily involved. One might describe the cutaneous manifestations of porphyria as "bullosis actinica et mechanica. In porphyria, even on the light-exposed surfaces, blistering is a late manifestation, and the Nikolsky phenomenon can be elicited irregularly if at all. To some extent, the degree of cutaneous reaction in porphyria may be proportional to the concentration of porphyrins in the tissues and to the kind of porphyrin that is concerned, as well as to the nature and concentration of the light source and the effect of its cumulative action. Photosensitivity is prominent in those cases in which porphyrins are injected experimentally into the skin and in cases of co genital porphyria, but it i rarely a feature of eithe chronic or acute porphyria.

The changes in the skins of patients with chronic porphyria involve the complexion and the dorsal skin of the hands (Brunsting et al J 146 1207 1951) There may occur diffuse melanosis of exposed skin and hair and discrete pigmented macules of the face forehead and arms. Auburn hair may turn black. The complexion characteristically becomes gradually dusky bluish red and the conjunctivae injected and bleary even in nonalcoholic patients. The beard is tough women tend to become hirsute The plethora and facies may superficially resemble Cushing s syndrome or polycythemia. The skin is easily traumatized, and occasional small blisters may appear on the face, ears or neck. Exposure to heat or light may incite pruritus. Histologic changes may suggest senile elastosis. Associated symptoms of abdominal colic or nervous disorder occasionally occur

Etiology—Mathews (APath 23 399 1937) in a classic review of photodynamic sensitization found that, in 32 reports which specified, porphyrinuria was present in 23 absent in 9

He stated that Raabe in 1900 showed that acridi e in a culture of i fusoria so altered them that light killed them. The effect is dependent upon the time of contact of the dye with the rganism. The action of ordinary light on sensitized prot plasm is similar to the action of ultraviolet of less than 3,100 A.U Eosin, erythrosin, fluorescein, bengal rose and the phylloporphyrin f buckwheat, as well as hematoporphyri have the capacity f sensitizing tissues. One can kill frogs by injecting them with eosin and exposing them to light. Hematoporphyrin is active when given by mouth, subcutaneously intramuscularly or by vein, but painting it on the skin does not photosensitize. Meyer-Betz gave himself 0.2 Gm. hematoporphyrin intra enously and was light sensitive for several weeks. Jodlbauer and Busch (1905) produced pruritus, edema, and even necrosis of the skin of the face and ears of experimental animals by so sensitizing them and exposing them to sunlight. By injection of eosin and exposure to sunlight, Quin (1933) prod ced symptoms of "bighead" in sheep; also, by tying the bile duct he found the icteric skin to be e been sensitized by bile-secreted phylloerythrin absorbed through the intestine from the hlorophyll rich diet. Such observations led Urbach and Block (WienKlinWchn 47: 577 1934) to believe that the presence of porphyrin signifies hepatic insufficiency

Animal photosensitization can result from diet, as in "fagopyrism from buckwheat "hypericism (the Arabs painted their horses with tobacco or henna to protect them from the sun when they grazed *Hypericum crispum*) "trifoliosis" from clover "tribulosis" from Sudan grass in South African sheep and goats, and "bighead" in sheep, and "goat fever" in southwestern United States; but no proof exists, Mathews said, that this occurs in man. Accidental sensitization of man has occurred with intravenous administration of acriflavine In pellagra, light sensitivity is an effect, not cause of the condition, Matthews believed. In eczema solare the appearance d disappearance of porphyrin depend on the appearance and disappearance of the dermatitis (Templeton and Lunsford: ADS 37: 849 1938)

Proof of the photosensitizational origin of the lesions of hydroa is lacking according to Blum and Lace (BJD 49 465 1937) and the assumption is untenable that all cases of abnormal sensitivity to light have the same cause. Their patient failed to develop lesions when exposed to those wavelengths to which porphyrins sensitize the skin The normal response to actinic irradiation is not porphyrinuria but in light sensitive patients irradiation may lead to marked increase in porphyrinuria Ill-defined endocrine and liver function *defects were present in 3 cases of extreme light sensitivity studied by* Morgan et al. (ADS 67 369 1953) who observed that some such patients follow queer diets.





Fig. 936—Hydroa vacciniforme vesicle formation and dermal inflammation
Fig. 937—Hydroa vacciniforme vesicle formed by separation of the outer layers of the epidermis, contains serum, leukocytes and fibrin dermis shows mild inflammation, with edema and vascular dilation (Dr Stuart C. W y)

The essay on porphyria by Turner and Obermayer (ADS 37 549 1938) is valuable Linser (AfDuS 79 251 1906) first recognized the frequent association of porphyria and hydroa aestivale Hematoporphyrin, possessed of notable photosensitizing power was once thought to be the porphyrin excreted in this disease Later it was learned that hematoporphyrin is never found either physiologically or pathologically

Porphyrins are constituents of hemoglobin and chlorophyll, and so are widely distributed in animal and plant life Animal porphyrins are red compounds which fluoresce red in ultraviolet light. Their spectral absorption bands are individually characteristic, but stereoisomers can be distinguished only by complex determinations of melting point of their methyl esters.

The naturally occurring porphyrins of importance are protoporphyrin, coproporphyrin, and uroporphyrin. Porphins, the basic nuclei from which porphyrins are chemically derived, are composed of 4 pyrrole rings united by 4(=CH—) groups, and each pyrrole ring has 2 replaceable hydrogen atoms. Four methyl and 4 ethyl groups replacing these constitute aetioporphyrin and form 4 series of compounds, of which only Types I and III occur naturally (Rimington ProcRoySocM 32 1268 1939; Edit BMJ 1: 1094, 1939) Hemoglobin comprises globin, a protein, combined with the iron-containing pigment, hematin, which is a porphyrin with an atom of iron bound to a nitrogen atom of a pyrrole ring by primary and secondary valences. The porphyrins differ in the positions of substituent groups on the porphin basic nucleus.

Protoporphyrins are derivatives of aetioporphyrins with 4 methyl, In I and propionic acid groups. Coproporphyrins are derivatives with 4 methyl d 4 propionic

acid groups. Uroporphyrins are derivatives with 4 methyl and 4 methyl malonic acid groups. Types I and III cannot derive from one another.

Of some 200 cases of hydroa, Turner and Obermayer (1938) stated that some 86 gave definite evidence of porphyria. Knowledge of porphyria, they noted, has been built largely around studies of one Mathias Petry whose "[illegible]" life of [illegible] years, biochemically busy ones, is biographied in a veritable medical library which includes a 360-page volume on his autopsy. The manifestations of hydroa in the presence of porphyria differ considerably, they believed, from those of hydroa without porphyria. Bullae are usually larger and do not show umbilication and recurrent attacks are accompanied with necrosis. Mutilations may become as extensive as in lupus vulgaris. In the presence of porphyria the disease persists as a rule throughout life while hydroa without porphyria may disappear spontaneously after puberty.

Hydroa is not the only dermatosis associated with porphyria. A number of cases *of epidermolysis bullosa have been so associated, and occasional cases of scleroderma,* calcinosis, keloid formation, xeroderma pigmentosum, lupus erythematosus and even hirsuties have manifested the association. Ocular complications have been noted, such as edema, crusting and scarring of the lids, ectropion, conjunctival scarring and, rarely, opacities of the cornea (Stokes: A Ophth 23: 1131, 1940).

In porphyria, hepatomegaly and disturbed liver function are not uncommon. Splenomegaly has occurred in several patients. Blood changes may include anemia as a significant feature presumably because erythrocytes are robbed of pyrroles needed for hemoglobin production. Blood studies, however, usually prove normal, and no evidence of disordered steroid metabolism is found, stated Brunsting et al. (1951).

In etiology influences detrimental to the liver are important, alcoholism being the main offender apparently responsible in 13 of the 17 patients of Brunsting et al. (1951). Diabetes mellitus, syphilis, arsenical intoxication and the use of barbiturates were factors in several patients in some of whom more than one cause appeared to be operative.

While the urine is often dark amber, it is sometimes pink and rarely red, while in some stages of the disease the urine might contain few or no abnormal porphyrins.

Coproporphyrin and uroporphyrin have repeatedly been demonstrated in the serum as well as in the urine. *The urine, generally described as red, ranges from pale pink to almost* black, or it may be normally yellow when passed but become dark after exposure to light through oxidation of porphyrinogen and urobilinogen.

Urinary porphyrins are almost always uroporphyrin and coproporphyrin I. Feces are not characteristic but tend to be dark reddish brown, turning dark on oxidation. While coproporphyrin and protoporphyrin are found in normal feces, coproporphyrin in porphyria may be enormously increased. The type of porphyrin excreted is of only slight diagnostic significance (Lang and Walker: BJD 65: 352, 1953).

Uroporphyrin and coproporphyrin are less active photosensitizers than hematoporphyrin. But whether their presence explains light sensitivity in hydroa is unproved. Lesions of hydroa are not identical with those of experimental porphyrin light sensitization *(Edlbow: BJD 47: 277, 1933), nor is there any uniformity of wave lengths of light to* which hydroa cases are susceptible, nor do efforts to provoke lesions with light always succeed, nor are all cases of hydroa associated with porphyria, but rather only the minority of them.

The changes in the skin in chronic porphyria may be influenced by the abnormal porphyrins which are produced when the liver is damaged by such a toxin as alcohol; or perhaps such a damaged liver may inhibit or destroy protective enzymes essential in the skin for the prevention of reaction to photosensitivity. The chief protection of the skin against light is probably the keratin layer but the value of pigment cannot be dismissed summarily, stated Brunsting and Mason (1947); the production of pigment in the human skin in cases of chronic porphyria is probably a late effect representing an effort to protect the underlying tissues from penetrating radiation.

The disease appeared to Brunsting et al. (1951) to be probably more common than is generally supposed. In recent years, physicians have become increasingly aware of the importance of the subject of porphyria. If careful search were made of members of families in which isolated cases of manifest porphyria occur, it is reasonable to suppose that a reservoir of cases of latent porphyria would be uncovered. It would seem that several different diseases of porphyrin metabolism exist (Wells and Rimington: BJD 65: 337, 1953).

Tests for Porphyrins, at least qualitative ones, are fairly simple (Brunsting and Mason, 1947). The urine is acidified with HCl and examined visually for fluorescence in a fluorophotometer, the beam being passed through a Corning filter 5113, giving maximum intensity at 4100 A.U. If red fluorescence is visible another sample of urine is acidified with acetic acid and extracted with ether to remove coproporphyrin. Residual red fluorescence which ether extraction does not remove from the aqueous layer indicates the

presence of uroporphyrin. Coproporphyrin is present in small amounts in normal urine and in excess in toxic diseases, especially those involving the liver. But the presence of uroporphyrin indicates porphyria. The type of porphyrin excreted does not, however, exactly define the class of porphyria present. In acute porphyria and in afflicted sibs, colorless porphobilinogen occurs in the urine and is thought a pathognomonic feature of the disease. Porphobilinogen is demonstrated by a modification of the Ehrlich-benzaldehyde test for urobilinogen, the urine being first extracted with chloroform. At times the urine of patients with porphyria may be entirely normal.

Quantitative porphyrin determinations were given by Zeligman (ADS 58: 281, 1948). See Turner (J 135: 394, 1947). Zeligman (ADS 61: 863, 1950).

Brunsting et al. (J 146: 1207, 1951) gave this method: Shake a sample of fresh urine which has been acidified with a few cc. of glacial acetic acid in a separatory funnel with an equal volume of the 1:1 mixture of normal butyl alcohol and ethyl acetate. Discard the aqueous phase after it has completely separated. Wash the alcohol-acetate mixture with 3 portions of distilled water. The organic-solvent layer will show red fluorescence in the near ultraviolet region of the spectrum. Then extract with 3 to 5 cc. portions of 10% NaOH; the porphyrins appear to go into the alkali almost quantitatively. Discard the alcohol-acetate mixture and neutralize the NaOH with HCL until the solution turns Congo red paper gray. Add 1 to 2 cc. of glacial acetic acid and shake the solution with an equal volume of ether. Coproporphyrin goes into the ether; if uroporphyrin is present, it will remain in the aqueous phase. If large amounts of porphyrin seem to be present, ether extraction can be carried out several times to insure removal of all of it from the water layer. Acidify the aqueous portion with HCL and examine it for red fluorescence in the light beam of the fluorophotometer.

Treatment.—In all of these conditions there is required protection from sunlight and trauma. Atabrine or chloroquine brought about excellent but unexplained improvement in 18 cases of light sensitive eruptions reported by Knox et al. (JID 22: 11, 1954), an observation confirmed by Cahn et al. (JID 22: 93, 1954). Some photodermatoses may have been successfully hyposensitized by increasing doses of ultraviolet light, Epstein (1942) noted, and ovarian follicular hormone or estrogen has helped some cases (Lain et al. SouthMJ 41: 1041, 1948). Hydrochloric acid, laxatives, antihistaminics and niacin may be tried. Alcoholism and hepatic dysfunction should be combated. Brunsting and Mason (J 132: 509, 1942) recommended procedures for protection of the liver as described by Snell (CalifM 63: 74, 1945). A pregnant patient with itchy lesions from porphyria reported by Linas (J 133: 105, 1947) improved post partum. Summer eczema associated with a low BMR yielded to thyroid medication, which often helps seasonal dermatitis, reported Hubbard and Martin (SouthMJ 33: 1312, 1940). Calciferol in a dose of 120,000 units per day, along with intravenous injections of calcium gluconate, produced dramatic response in a patient of Nexmand (ActaD-V 31: 572, 1951). The antihistamine drugs, particularly Pyribenzamine, are helpful, especially in photogenic urticaria. Potassium para-aminobenzoate 1 Gm. t.i.d. for 4 days served to prevent activity of hydroa vacciniforme for a long time in the boy seen by Zarafonetis et al. (JID 21: 5, 1953).

Other Dermatoses Associated With Light Sensitivity.—See Contact photosensitization. Dermatitis medicamentosa (sulfonamides). Xeroderma pigmentosum. Lymphopathia venerea. Senile keratoses. See Stokes and Beerman (AmJMedSci 204: 801, 1942) on photodynamic effects. Absorption of phenothiazine, which has been used to spray orchards and to control helminthic infections of livestock, may induce photosensitivity (De Eds et al. J 114: 2095, 1940; see J 130: 183, 1946).

See Hausmann and Haxthausen (Die Lichterkrankungen der Haut, Strahlentherapie, Urban & Schwarzenberg, 1929, vol. 11). Blum (PhysiolRev 12: 23, 1932), review and bibliography. Seidel (ArDS 174: 177, 1936), hydroa not directly caused by porphyrin. Vannotti (Porphyrine und Porphyrinkrankheiten, Springer, 1937), chemistry. Tropea (ArDS 177: 112, 1938), irradiation of light-sensitive individual caused marked porphyrinuria. Turner (AIntM 61: 762, 1938), acute case simulating lead poisoning, alleviated with intravenous calcium. Urbach (KlinWchr 17: 294, 1938), cases of photosensitivity following liver damage. Epstein (Dermatologica 80, no. 5, 1939), review and bibliography. Blum (Photodynamic Action and Diseases Caused by Light, Reinhold, 1941). Arnold (ADS 43: 407, 1941), technic of determining etiologic wave length in solar urticaria. Watkins (ArchPhysTher 24: 291, 1943), urticaria due to heat of 7,000 to 14,000 A.U. Hrabina (BJD 56: 195, 1944), case, scaling on exposed parts following electric welding. Sulzberger and Baer (JID 6: 345, 1945), photosensitivity limited to an irradiated area, patient's serum passively sensitized normal individuals; Tyson (JID 7: 209, 1946), woman with dysmenorrhea and solar urticaria worse during periods, relieved by Benadryl. Kock (Dermatologica 92: 149, 1946), chronic porphyria in woman with hydroa vacciniforme. Jorgensen and With (abs J 131: 74, 1946), barbiturates may aggravate chronic porphyria. Taylor et al. (J 131: 26, 1946), differential diagnosis of congenital, acute and chronic porphyria. Gomez and Castro (Dermatologica 94: 327, 1947), porphyria excretion, quantity unrelated to degree of photosensitivity and niacin increased porphyrin excretion, improved tolerance of light. Zeligman and Baum (ADS 58: 357, 1948), case relating porphyria and acquired epidermolysis bullosa. Watson (BMJ 2: 574, 1950), case, pemphigus foliaceus, folic acid prevented abnormally high excretion of coproporphyrin. Macgregor et al. (AIntM 90: 483, 1952), chronic case observed during 3 major attacks, with photosensitivity, hydroa, colic, hypertension and jaundice during them, and chemical studies showing association of hypertension and increased urinary output of uroporphyrin. Barnes and Marshall (AnnderD 79: 681, 1952), congenital porphyria in South African natives. Kaplan and Barton (ADS 67: 584, 1953), review and classification of light-sensitivity diseases, data on chemical sensitizers. Calvert and Rimington (BMJ 2: 1131, 1953), case, "tarda" type, severe colic and polyneuritis with attacks. Duncombe and Trelp (BMJ 2: 1134, 1953), attack associated with

weakness resulting in inability to breathe; Wells and Rimington (BJD 65: 337 1953) familial "tarda" case, skin reaction to carbon arc light with high emission between 3800 and 4100 A.U. Pettit and Anderson (BJD 65: 386, 1953) sisters with melanosis, hypertrichosis, bulla formation and lesions on legs resembling lichen chronicus simplex. Cahn et al. (JID 21 375, 1953) relation of polymorphous light eruptions to lupus erythematosus; Dean (BMJ 2 1291, 1953) familial porphyria common in South Africa, severe attacks sometimes being precipitated by barbiturates; Beason et al. (BMJ 1; 944, 1954) delayed, light-sensitive, bullous cases, nonfamilial, in adult males, chemical study, Woodburn et al. (ADS 70 116, 1954) Atabrine helpful in all types of solar dermatitis. Holgert and Conlvet (BJD 66 313, 1954), 17 cases, cutaneous in adult. Michelson (AD 71: 638, 1955) review, Vannotti (Porphyrins Their Biological and Chemical Importance, transl. by Rimington, Hilger and Watts, London, 1954)

AVITAMINOSES

The fact that disease may result from the lack of something has been appreciated only recently (Haden J 106 261, 1936) The skin as well as other organs, exhibits changes due to nutritional inadequacy which may result from insufficient supply at the site of absorption, or from inability to utilize the substances or to convert them into assimilable forms, or from excessive requirement because of infection, pregnancy or metabolic peculiarity such that the individual demand exceeds that amount which usually suffices to prevent symptoms of deficiency To fulfill its purpose, a nutritional factor not only must reach its point of use in sufficient amount but also must actually be used there. In the macrocytic anemias, pellagra, neuritis of pregnancy pellagra and alcoholism the major defect lies as a rule in absorption rather than in supply (Strauss J 103 1 1934) The possible disparity between the quantity of nutrients eaten and the amount absorbed cannot be ignored (Edit J 140 1160 1949) even under normal conditions.

Solitary dietary faults are the exception, for in deficiency conditions there is often a complicated interlinking of one substance with another (Spies et al AmJMedSci 200 536 1940) The full blown deficiency diseases are usually recognized, but the minor symptoms of deficiencies that are common are regularly missed unless kept in mind and searched for Glossitis or an atrophic tongue as well as peripheral nerve disturbances, should always bring to mind vitamin B deficiency Easy bruising and unexplained edema should make one think of a deficiency in vitamin C

The idea of specificity of the various vitamins was more prominent in the past than it is now for new conceptions are evolving of coordination or interdependence of action among the vitamins (Edit: J 138: 104-, 1948) Symptoms formerly thought characteristic of avitaminosis C may appear under conditions of lack of A (Mayer and Krehl: ABiochem 16: 313 1948) while the addition of C to the A-deficient diet corrects the scorbutic symptoms. Withdrawal of A from the diet may result in diminution of the blood level of C. In experiments using rats on A-deficient diets, changes little resembling phrynoderma were observed by Ramalingaswami and Sinclair (BJD 65: 1, 1953) but the lack of essential fatty acid produced changes resembling those of so-called avitaminosis A.

Vitamin Deficiencies were epitomized by the Council on Foods and Nutrition of the A.M.A. (J 131 666 1946) "Deficiencies of several vitamins, notably biotin, pyridoxine pantothenic acid and vitamin E, are not accompanied by stigmas which can be recognized at present. The subject is in a stage of fluidity and development which will necessitate early revision or amplification. Particularly is this true of the diagnosis and treatment of deficiency of folic acid. Not many of the stigmas listed are diagnostic of a vitamin deficiency in themselves, but the occurrence of several of these stigmas in association is at least presumptive evidence of some nutritional failure. Vitamin deficiencies commonly encountered in clinical practice are multiple Scrutiny of the dietary history is indicated in cases in which several of the stigmas listed are present. Treatment for a deficiency involves administration orally or if need be, parenterally of large enough doses of the vitamin to be of therapeutic value and continuation of this treatment for long enough periods to assure a satisfactory therapeutic trial. However since the diagnosis is necessarily presumptive in many instances exclusive dependence on specific therapy is justified only infrequently and basic to good treatment in all cases is a diet planned to be adequate nutritionally and assurance that the diet is eaten. Likewise helpful in treatment because of its content of fac

tors not as yet identified is some good source of the vitamin B complex as a whole. Products such as brewer's yeast or an extract of such yeast, wheat germ, extracts of cereal grasses or of rice bran, crude extract of liver or desiccated liver represent such sources. For a patient who cannot take foods or drug orally or in whom absorption is poor, crude liver extract may be given intramuscularly or even on occasion it may be diluted with sterile isotonic solution of sodium chloride or dextrose and administered by vein.

STIGMAS SUGGESTING DEFICIENCY OF VITAMIN A

Xerosis of the conjunctiva
Thickening with loss of transparency so that only the more superficial vessels of the bulbar conjunctiva are clearly seen, associated with more or less yellow pigmentation, especially along the horizontal meridian of the eyeball. Infrequently associated with small foamlike plaques called Bitot's spots.

Papular eruption of pilosebaceous follicles
A grater-like feel, which in early stages resembles gooseflesh but, when more fully developed, presents the picture of keratosis pilaris. The extensor surfaces of the arms and thighs and the flexor surfaces of the legs are primarily affected.

Xerosis or asteatosis of the skin
Dryness, scaliness and crinkling, in extreme cases resembling alligator skin. In early stages the condition is associated with keratosis pilaris but it persists and extends after follicles have disappeared, the body hairs being broken and later lost. All parts of the body are involved, but the skin of the extremities, particularly of the legs, is more severely affected than the skin of the head and the trunk.

Follicular conjunctivitis
Hypertrophy of the follicles, particularly of the lower eyelids.

Night blindness
Conspicuous only in cases of advanced, severe deficiency.

Keratomalacia
Thickening with subsequent ulceration and necrosis of the cornea, present only in most severe and advanced forms of deficiency.

TREATMENT OF VITAMIN A DEFICIENCY

Early deficiency state
25,000 U. S. P. units of vitamin A twice daily for 3 months or longer.

More chronic state
25,000 U. S. P. units of vitamin A 2 to 3 times daily for a prolonged period.

STIGMAS SUGGESTING DEFICIENCY OF RIBOFLAVIN

Congestion of the limbic plexus
Visible with a small hand lens or the +20 lens of the ophthalmoscope. Invasion of the cornea by capillaries arising from this plexus (vascularization) requires a biomicroscope and slit lamp for detection.

Cheilosis
Represented in chronic deficiency by excessive and irregular wrinkling. In acute deficiency by swelling and erasure of the normal wrinkling of the lips. Reddening, thinning, scaling, chapping of epithelium are associated.

Angular stomatitis
Various combination of erythema and open fissuring in the angles of the mouth with or without white moist maceration (perlèche); scars of healed fissures.

Dyssebacea
An erythema ... with somewhat greasy flaky accumulations resembling hoar frost, noted mostly in the alae nasi, canthi, pinnae and other folds of the skin, accompanied in some cases by coarsening and elevation of the sebaceous follicles of the nose and cheeks, the latter also seen with deficiency of vitamin A.

Magenta tongue
A purplish red coloring with moderate edema and flattening of filiform papillae, observed in more advanced deficiency.

TREATMENT OF RIBOFLAVIN (B_2) DEFICIENCY

Acute deficiency state
5 mg. riboflavin 3 times daily for weeks.

Chronic deficiency state
3 to 6 mg. of riboflavin 3 times daily for a prolonged period.

STIGMAS SUGGESTING DEFICIENCY OF NIACIN

Edema of the tongue
Shown by dental indentations.

Increased redness of the tongue
Beefy red in chronic states, scarlet red in severe acute deficiency.

Congestion and hypertrophy of the papillae of the tongue followed by fusion and atrophy
In early stages the fungiform papillae are congested and hypertrophied. This is followed by hypertrophy of the filiform papillae and later by their flattening. As they atrophy they fuse or mat together with multiple fissuring to give a cobblestone appearance and finally baldness. Vincent's infection of tongue and fauces, ulceration and pseudomembrane formation may or may not accompany these changes in the more advanced stages of this deficiency.

Dermatitis
Erythema, rough scaling, with ulceration and formation of bullae, affecting primarily areas of the skin exposed to light, namely wrists, ankles, neck and face, observed only in severe deficiency (pellagra) and then frequently associated with diarrhea and dementia.

Encephalopathy
Clouding of consciousness, cogwheel rigidity and grasping, sucking reflexes observed in acute severe deficiency.

TREATMENT OF NIACIN DEFICIENCY

Acute deficiency state
100 mg. or more of nicotinamide twice daily for weeks.

Chronic state
100 mg. of nicotinamide twice daily over a prolonged period.

STIGMAS SUGGESTING DEFICIENCY OF ASCORBIC ACID

Redness, edema, tenderness and bleeding on pressure of the gums
Observed in acute, or subacute deficiency of moderate severity sometimes with, but usually without, other signs of ascorbic acid deficiency.
Thickening and increased firmness of the gums
With recession and exposure of the base of the teeth, including recession of interdental papillae; observed in chronic deficiency.
Retraction of the gums
Leaving pockets between gums and tooth, secondary infection and resulting pyorrhea; observed in chronic deficiency.
Loosening and shedding of the teeth.
Increased capillary fragility
Manifested by petechial hemorrhages of the skin, especially in the tourniquet test; observed in more severe acute and subacute deficiency. Easy bruising, spontaneous ecchymosis of the skin, idiopathic hemorrhage into joints and slow healing of wounds, observed in severe acute and subacute deficiency.

TREATMENT OF ASCORBIC ACID DEFICIENCY

Acute or subacute deficiency state
100 mg. or more of ascorbic acid per day for weeks.
Chronic deficiency state
100 mg. of ascorbic acid 3 times daily over a prolonged period.

STIGMAS SUGGESTING DEFICIENCY OF VITAMIN K

A tendency to bleeding
Particularly from minor wounds, related to abnormal lengthening of the prothrombin time, developing spontaneously in newborn infants; observed in adults after treatment with Dicumarol or large doses of salicylates; in advanced disease of the liver with poor excretion of bile, and in diseases of the intestine, such as sprue, in which vitamin absorption is disturbed.

TREATMENT OF VITAMIN K DEFICIENCY

In adults
1 mg. of vitamin K 2 to 3 times daily with or without bile (1 Gm. of desiccated bile or bile salts).
In newborn babies
1 mg. of synthetic vitamin K intramuscularly daily in oil solution for several days.

DEFICIENCY SYMPTOMS

A diagnosis of vitamin deficiency only rarely can be based on symptoms or less significant abnormalities than those which have been listed. However such symptoms and abnormalities frequently accompany the more specific lesions of deficiency.

Symptoms commonly observed with deficiency of thiamine, also less conspicuously in deficiency of other vitamins, include apathy, lethargy, increased emotional irritability, hypersensitivity to noise and painful stimuli, headache, vague fears, confusion of thought, uncertainty of memory, asthenia, loss of manual dexterity, insomnia, heart consciousness, paresthesia, anorexia, nausea, flatulence, epigastric pain, constipation. Photophobia, burning of the eyes, lacrimation and eyestrain not relieved by glasses are encountered in deficiency of riboflavin. Other abnormalities unrelated to deficiency of any single vitamin but commonly observed in persons who are malnourished are dry, brittle, lack-luster, rebellious, so-called staring head hair, a loss of sleekness analogous to the rough coat of malnourished animals, blepharitis, spiderlike telangiectasis of the face, seborrhea of the face, patchy pigmentation of the face, especially suborbital and circumoral, sinus arrhythmia, bradycardia, tachycardia, low blood pressure, loss of tone of muscles and anemia.

FACTOR	NEEDED FOR INTEGRITY OF
Vitamin A	epithelial tissues
Vitamin B_1	nerve tissues
Vitamin B_2 (G)	dermal tissues
Vitamin C	endothelium of blood vessels

SYSTEM	LESIONS OF DEFICIENCY
Epithelium	Atrophy, scaling, dermatitis, pigmentation, ulceration, cornification
Nervous system	Neuritis, pain, paresthesia, weakness, paralysis Degeneration of spinal cord Tetany
Alimentary tract	Anorexia, stomatitis, glossitis, atrophy of tongue, achlorhydria, loss of specific ferments, diarrhea, loss of tone of gastro-intestinal tract, ulceration of intestine
Hematopoietic system	Macrocytic anemia, hypochromic anemia, microcytic anemia
Vascular system	Hemorrhage, easy bruising, edema

Antivitamin Activity of certain chemical compounds closely related to the various vitamins is a well-established fact (Edit J 134 1550, 1947). Woolley (PhysiolRev 27: 308 1947) stated that there is at least one known antivitamin for each of the water-soluble vitamins and for 2 of the 4 fat-soluble ones. Pyrithiamine when given to mice or rats is followed by classic symptoms of thiamine deficiency and the effect is nullified if sufficient thiamine is administered. Indole acetic acid has an antiniacin influence (Kodicek et al. Lancet 2: 491 1947); it was isolated from corn and may be related to the relative prevalence of pellagra in corn-eating populations. The structure of the antivitamin is such that it competes with the metabolite; substituting a sulfonic acid or a ketone for a carboxyl group might make the change but

no one way of changing the molecule is essential. The practical significance of these substances is confined to experimental therapy of the lymphoblastomas, where folic acid antagonists have been found sometimes palliative in leukemia (q v) and in investigative medicine.

Vitamin A Deficiency (Phrynoderma).—The dry shrivelled and scaly skins of infants with nutritional ophthalmia were observed by Bloch (J Hyg 19 283 1921) who showed that some fats contain specific, indispensable



Fig 938.—Cutaneous lesions in vitamin A deficiency general xeroderma and follicular hyperkeratosis in a Chinese patient with xerophthalmia, before halibut liver oil therapy had been given. Photomicrograph shows hyperkeratosis of a hair follicle in vitamin A deficiency (Dr Chester N Frazier)





Fig. 939.—Avitaminosis A groups of hyperkeratotic papules overlie joints. (Frazier and Hu: ADS 33 825, 1936.)

Fig. 940.—Changes in the skin of the breasts in avitaminosis A. (Dr A Hill)

bodies, the absence of which leads to xerosis, night blindness and keratomalacia. Reporting an epidemic of keratomalacia in children's homes, Cramer (Lancet 1 633 1924) performed animal experiments, successful in producing ocular lesions, emaciation and atrophy of the lacrimal and intestinal glands. In guinea pigs fed an A-deficient diet Wolbach and Howe (APath 5 239 1928) observed that the epithelium of the lacrimal glands, bladder uterus and elsewhere underwent squamous metaplasia. These changes had been found in a human infant suffering from keratomalacia by Wilson and DuBois (AmJ DisChild 26 431 1923)

The patients of Frazier and Hu (ADS 33 825 1936) were Chinese soldiers who presented ocular evidence of avitaminosis A and eruptions resembling keratosis pilaris. Spinous papules appeared at the sites of hair follicles, first over the anterolateral aspects of the thighs and posterolateral aspects of the arms then spreading over the extremities, shoulders, lower abdomen and, to a lesser degree over the chest, back and buttocks. The flexures were dry and scaly and in some instances the skin assumed a dirty slate color Occasional atrophic ulcers appeared. The microscope revealed hyperkeratinization of epidermis and follicles and squamous metaplasia of sweat duct epithelium. There were atrophy of the hair bulbs and cystic degeneration of some of them. These symptoms were relieved slowly when the diet was properly altered.

Sweet and K'ang (AmJDisChild 50 699 1935) showed similar horny papules in the pilosebaceous follicles of their cases. Acneiform lesions, dry skin, folliculitis, pruritus and xerophthalmia were seen in Uganda prisoners by Loewenthal (ADS 28: 700 1933), and were cured by taking cod liver oil. Follicular hyperkeratoses with small perifollicular petechiae were noted in scurvy by Sheer and Kell (ADS 30: 177 1934)

The pathology of avitaminosis A was reviewed by Wolbach (J 108: 7 1937) who showed that in spots there occurs an undermining with stratified squamous epithelium which spreads and replaces the normal. The skin and conjunctivae in A-deficiency contain melanophores and pigment, which is diminished about the follicles but increased in the hyperplastic epithelium; old pigment is cast off in the scales. Changes vary with age, young individuals showing mild xerosis and adolescents manifesting greater evolution of follicular lesions (Frazier et al.: ADS 48: 1 1943)

Jeghers (J 109 756 1937) put himself on a diet lacking vitamin A: after 5 weeks he had night blindness but no xerosis and when he resumed the intake of vitamin A his sight improved within 3 hours, and he was cured in 3 days. A prolonged human experiment, utilizing 23 young conscientious objectors as subjects, showed in most of them early rapid depletion followed by slower depletion, but deterioration of dark-adaptation was found in only 3 all of whom had less than 40 units of plasma vitamin A. There occurred no other symptom ascribable to A-deficiency and the plasma vitamin A fall was preventable by giving only 2,500 units per day (Edit BMJ 2: 932, 1950)

Phrynoderma (toad skin) was common among the Tamils of the Federated Malay States, Fasal (ADS 50: 160, 1944) reported. Many of his patients showed Bitot spots, white triangular lesions of the lateral sclera which probably are due to avitaminosis. Red palm oil proved a cheap and effective source of vitamin A for these people. A child with localized xerophthalmia (Bitot spots) of the conjunctiva and skin lesions of follicular hyper keratosis responded to the administration of vitamin A (Marmelzat: ADS 63 759 1951)

Acneiform, comedo-like, noninflammatory lesions were the feature of children studied by Youmans and Corlette (AmJMedSci 195 644 1938) Keratosis pilaris, lichen pilaris, lichen spinulosus, and ichthyosis follicularis seem merely different names for avitaminotic lesions, in the opinion of Lehman and Rapaport (J 114: 396 1940) Response to vitamin A therapy in a dose of from 100 000 to 300 000 units per day requires 2 to 4 months. Hecht and Mandelbaum (AmJPhysiol 130 651 1940) likewise found 6 weeks or more requisite to recovery from visual threshold defects. Nail changes in avita

minosis A comprise thinness and fragility longitudinal ridges transverse bands and punctate pits, which ceased to appear in White's patients (J 102 2178 1934) when Haliver oil was administered. Conjunctival folliculosis responds to vitamin A administration (Sandels et al. AmJDisChild 62 101, 1941)

The lack or abundance of vitamin A had no effect on the susceptibility of rats to coccic infection of the skin, discovered Sternberg and Pillsbury (ADS 35 247 1937) No relation between vitamin A and skin infection in the human being could be discerned by Novy (CalifWM 56 144 1942)

THE PHYSIOLOGY OF VITAMIN A UTILIZATION was summarized (Bessey and Wolbach J 110 2072, 1938) as follows No vertebrate can synthesize carotenoids. Vertebrates probably can convert some carotene into vitamin A. Carotene is provitamin A of which there may be 4 forms, alpha, beta gamma, delta. Proper assimilation of carotene is dependent on the normalcy of fat metabolism. Absorption of carotene is disturbed by diarrhea, celiac disease and other disturbances. Habituation to mineral oil perhaps interferes with absorption of carotene but not of vitamin A Eggs milk and fish liver oil are rich sources of vitamin A. Colostrum is 10 to 100 times as potent a source as milk. The plasma carotenoid content is a measure of the difference between the rate of absorption and the rate of conversion of carotene int vitamin A. If carotene is injected into a vein it is fast removed by the reticulo-endothelial system and pigment granules can be found in the Kupffer cells, which store vitamin A. Blocking the reticulo endothelial system causes diminution in the capacity for storage but poisoning with phosphorus, which destroys liver cells does not diminish the capacity to store vitamin A. Phosphorus poisoning does diminish the ability to convert pro itam n into vitamin.

Antagonism between vitam n A (and caroten) and thyroxine was discussed by Clausen (J 111 144 1938) Animal losing weight because of daily injecti ns of thyroxine were kept from losing by the coincidental administration of carotene Injections of thyroxine decreased the stores of carotene and vitam n A in the liv rs of guinea pigs. Goats on normal diets had white coats until their thyroid gland ere removed, and then the coat became yellow because of the presence of carotene although th di t was unchanged. In cretinism the plasma i deficient in vitamin A; and if carotene is given, the deficiency nevertheless persists fo t is not utilized properly in hypothyroidism. In hyperthyroidism the plasma cont nt of vitamin A is low because it is destroyed; but if iodine is administered or t successful surgery is undertaken, the concentration of vitamin A in the plasma in eases. Experiment in vitro indicate that thyroxine is destroyed by ca otene hyperthy o d sm can be treated by gi ing huge doses of v tamin A

During i fections carotene and also itamin A are poorly absorbed. Investigations of the blood content of itamin A and of arotene in variou dermatoses were reported by *Marchionini and Patel (AfDuS 175 419 1937) Many cases of dermatitis had zero to* trace alues, which are low Normal values occurred in pyogenic diseases W despread dermatoses, su h as eczema psoria and ultraviolet dermat ti were a sociated with low values. High l ls occ rred in xanthoma. The authors were aware f the ever-present problem of determining which comes first the dermatosis or the chemical alteration in the blood.

Vitam n A deplet on occurs in steatorrhea (Albright and Stewart NEngJM 223: 239 1940) It is doubtful whether petrolatum laxatives cause deficiency (Curtis and Ballmer *J 113 1785 1939) Isaacs and Jung (PIMChi 1 : 206 1940) could not detect it.* Lacking v tamin A osteoclastic and osteoblastic activity is diminished, and the resultant dysplasia of bone produces grave effects on the nervous system, cranial nerves I II V and VIII suffering most (Mellanby JPhy ol 103 382 194)

Vitamin A disturbances often accompany thyroid dyscrasias, fo the hypothyroid individual fails to utilize A and the hyperthyroid uses it excessively Skin manifestations are well described and illustrated by Platt (BritJHBull 3 159, 1945) V tamin A chemistry is discussed by Butt (J 120 1030, 194) ts synthesis b Milas (Sci 103 581 1946) Oral administrat n is simple and p obabl n mor effective than parent ral n the verage case (Lease JLabCl nM 2 30 1943)

Mineral Oil and Avitaminosis.—The habitual use of mineral oil as a laxative probably interferes with the absorption of nutrient from the intestine, but the extent to which it does so is probably not significant (Edit J 107 1656 1936) As a solvent it tends to remove the oil-soluble vitamins from the intestinal content (Council on Foods J 109 1814, 1937) It lubricates the rectosigmoid making a reservoir of the rectum and prevents complete evacuation of the bowel, and by hastening the motility of the intestinal contents it prevents completeness of digestion thought Morgan (*AmJSurg* 42 360 1938) The absorption of mineral oil from the gut is known to occur and it may have harmful effects on the liver Carotene is not absorbed when

mineral oil is given, but vitamin A is, according to Curtis and Kline (AIntM 63: 54 1939) The mineral oil habit is an undesirable one although specific ill effects on the skin, healthy or diseased, are unproved.

See Acne, treatment Darier's disease Pityriasis rubra pilaris; Holmes and Corbet (Sci 85 103, 1937), crystalline vitamin A, 3,000 000 u/Gm.; Palmer (J 110 1748, 1938) chemistry Roeber (J 110 1920, 1938) bile essential for utilization, liquid petrolatum inhibits absorption of carotene Schneider and Widder (ArchPath 178: 148 1935) A and carotene in various dermatoses Straminger et al. (J 113 2381 1939) normal serum measurements Moult (ADS 47 762, 1943) histology of skin changes in rat W Hamy and Schraffenberger (AOphth 35 150, 1946) A-deficiency and congenital eye defects Edit (J 132 287 1946) carotene and A-metabolism

Hypervitaminosis A was shown by Toomey and Morissette (AmJDisChild 73 473 1947) to have been the cause of oily scaly rough, itchy skin and painful swellings of the extremities, anorexia constipation and irritability of a young child. Chronic intoxication was first reported by Josephs (AmJDisChild 67 33 1944) whose patient had received some 240 000 units per day for many months, and who showed poor appetite enlargement of the liver and spleen clubbed fingers and dry coarse scant hair X ray studies showed irregularities of the cortex of the phalanges and metacarpals, vacuolated medullary cavities, mottled epiphyses of the humeri and tibiae and advanced bone age. Immediate improvement followed cessation of the drug Subacute intoxication of a man was reported by Mouriquand (PresseM 56 737 1948) with irritability vertigo headache and vomiting resembling those induced by the ingestion of polar bear liver Generalized pruritus was among the symptoms in the case of Wyatt et al. (J 144 304 1950)

In infants, acute hypervitaminosis A will cause transitory and ultimately harmless distress requiring prompt diagnosis and withdrawal of the drug There occur acute hydrocephalus with bulging of the fontanel, vomiting agitation and insomnia beginning within 12 hours and ending in 48 hours (Marie and See AmJDisChild 87 731 1954; Hooft: abs J 156: 1460 1954) from doses ranging from 100 000 to 600 000 units.

The bone changes studied in vitro by Fell and Mellanby (BMJ : 535 1950) were mainly in the nature of periosteal proliferation in the human being, according to Grand and Fried (AmJDisChild 79: 3 475 1950)

Polar bear liver apparently owes its toxicity to its high content of vitamin A (Rodahl and Moore Biochem J 37: 166 1943) for it contains about 15,000 u/Gm. and a pound would contain some 7,500 000 units, sufficient if ingested in one meal, to cause extreme illness (QMN 143: 600 1950) Drowsiness sluggishness, headache vomiting diarrhea and collapse along with erythema and peeling first about the mouth sometimes universal, have long been known to explorers of the Arctic to occur if this food is eaten in desperation, and it poisons dogs as well as human beings (J 118: 1026, 1942 128 541 1948) When freed from its vitamin A content, polar bear liver is no longer poisonous (Rodahl: JNutrit 41 399 1950), and the administration of an equivalent amount of crystalline vitamin A has similar toxic effects.

See Edit (J 143 1417 1950) Caffey (Pediat 5 672, 1950), cases; Caffey (AmJRoentg 65 12, 1951) x ray changes Gribetz et al. (Pediat 7 372, 1951) cases, Sulzberger and Lazar (J 146 788, 1951), case in adult Ilineberg and Gross (J 146 1222, 1951), case infant Bair (J 146 1573, 1951) cortical and cranial hyperostoses; Bifalco (NEngJM 242 690, 1950), alopecia, insomnia, listlessness, headache, bleeding tendency in adult Cohlan (Sci 117 535, 1953) production of congenital anomalies in rats with overdosage of A.

The Water-Soluble Vitamins were known in 1942 to include at least the following factors (Elvehjem J 120 1388 1942)

thiamine (B_1)—antineuritic
riboflavin (B_2 or G)—antiperlèche and growth factor
niacin (P P, nicotinic acid)—pellagra preventive
pyridoxine (B_6)—rat antidermatitis factor
pantothenic acid (filtrate factor)—needed by all living things
biotin (H)—anti-egg white injury factor
para aminobenzoic acid—antigray hair factor
inositol—mouse antialopecia factor
choline—growth factor needed for formation of methionine
ascorbic acid (C)—antiscorbutic
citrin (P)—hesperidin and demethylated hesperidin (eriodictin); antihemorrhagic
grass juice and milk factors—essential for guinea pigs
L. casei factor—antipernicious anemia factor (see Folic acid)

From this list of 13 factors, Elvehjem (J 138 960 1948) removed 3 citrin the grass juice and milk factors essential for guinea pigs, and vitamin C for The vitamin B complex is usually differentiated from the other water-soluble vitamins, such as vitamin C and related factors on the basis of the source material used in early isolation work and the kind of experimental animals employed for the assay Elvehjem (1948) added B_{12} to the 10 remaining members of the B complex with which a pure compound had by that time been associated.

Thiamine (Vitamin B) —In pellagra (q v) administration of B_1 relieves the neuritic element but does not influence dermatitis or stomatitis (Williams and Spies Vitamin B_1 Macmillan 1938) B_1 is concerned with carrying carbohydrate metabolism beyond the pyruvic acid stage where it is halted in the absence of the vitamin (McHenry Sci 86 200 1937) The natural sources include the legumes, nuts, whole grains, egg muscle and visceral organ meats and milk (Munsell J 111 927 1938); see Booher (The Vitamin B Content of Foods, U.S Govt Printing Off., 1939)

Lack of this nutrient is not known to cause dermatologic manifestations. The usefulness in dermatologic therapy is slight although it has been given in herpes zoster and tabetic crises with alleged benefit It is nontoxic in a dose 25 000 larger than that which is required (Cowgill J 110 805 1938)



Fig 261 —Cheil tis n ariboflavinosis associated with cirrhosis of the liver (Dr B. Gill)

Riboflavin (Vitamin B_2) —As a complex, B_2 was formerly considered at least quadripartite including nicotinic acid riboflavin, a rat antidermatitis factor and a chick antidermatitis factor (Nelson J 110 645 1938) Deficiency in rats causes atrophy of the sebaceous glands and epithelium of the tail, with hyalinization of connective tissues (Smith and Sprunt JNutrit 10 481 1935) Rats lacking B are subject to louse infestation and this is curable by correcting the deficiency (György PSExperBiol 38 383 1938) Though nontoxic, it proved ineffectual in relieving human pellagra reported Hogan (J 110 1188 1938)

Riboflavin deficiency was clarified by Sebrell and Butler (PHRpts 54 2121 1939) who induced the condition experimentally and observed the development of a reddened denuded lesion of the lips, maceration and fissuring in the angles of the mouth, and seborrheic accumulations at the nasolabial folds. These manifestations appeared after approximately 3 months and were curable and preventable by the administration of pure riboflavin. Oden et al. (PHRpts 54 790 1939) and Sydenstricker et al. (J 113 1697 1939; 114 2437 1940) confirmed these findings and described an additional feature comprising characteristic lesions of the cornea, with photophobia and dimness of vision not relieved by refractive correction, burning of the eyeballs and roughness of the lids and extreme visual fatigue Circumcorneal injection progressed to *superficial vascularization* of the cornea, starting at the limbus, and riboflavin, 5 to 15 mg per day specifically relieved the condition. This

type of keratitis is, according to Sydenstricker et al. (SouthMJ 34 165 1941) the earliest and commonest visible manifestation, which had been noted in rabbits by Bessey and Wolbach (JExperM 69 1, 1939)

When riboflavin was withheld from human beings, there developed seborrhea, scrotal dermatitis, angular stomatitis, fissuring of the ala nasi, seborrheic patches, cheilosis, even lichenification and perhaps burning and itching, in the experiments of Hills et al. (AIntM 87 682 1951) Yet no circumcorneal injection or vascularization appeared and glossitis was not observed Jolliffe et al. (NEngJM 221 921, 1939) described filiform excrescences arising from the sebaceous glands of the face in skin areas showing a greasy fine desquamation. Cheilitis and perlèche were also frequently present in their patients.

Riboflavin is valuable in rosacea (q v); see also stomatitis, metabolic.

See Booher (J 110: 1105, 1938) chemistry; Sherman and Lanford (J 110 1278 1938) sources and requirements Johnson and Eckhardt (AOphth 24 1001, 1940) ocular symptoms Spies et al. (AmJMedSci 200 697 1940), endemic ariboflavinosis in children; Kruse et al. (PHRpts 55: 157 1940) ocular manifestations; Lanford et al. (JNutrit 21: 175, 1941) riboflavin content of fruits Hou (ChinMJ 59: 314 1941) cheilosis and seborrheic dermatitis in Chinese; Edit (BMJ 2: 110, 1943) complexities of various manifestations; Crowe et al (BiochemJ 40 458, 1946) interdependence of B_1 and riboflavin; Stern and Lande (AmJOphth 31 1619 1948) eczematous keratitis.

Nicotinic Acid.—See Pellagra.

Pantothenic Acid and Para-aminobenzoic Acid (the antigray hair vitamin) are further members of the B complex. Actual antigray hair value of these when given for that purpose to human beings is highly dubious (Edit J 122, 875 1943) Brandaleone et al. (PSExperBiol 53 47, 1943) obtained little improvement in the treatment of grayness of the hair in human beings given intensive vitamin therapy No specific symptoms in human beings have been correlated with a deficiency of pantothenic acid, perhaps because of its wide distribution and the adequacy of its supply even in restricted diets (Elvehjem, 1948)

Pyridoxine (Vitamin B_6) prevents an acrodynia like condition of rats with alopecia of the paws and about the mouth. Its administration seemed occasionally helpful in various eczematoid conditions in which it was tried by Wright et al. (ADS 47: 651 1943) A syndrome of itchy patchy superficial, vesicular and scaly erythroderma with macrocytic anemia was reported by Stryker and Halbeisen (ADS 51 116 1945) Lesions occurred on the face, neck and upper part of the chest and resembled pellagra, neurodermatitis or venenata. Improvement was usual when the patient received a good diet, pyridoxine and injections of crude liver extract.

No clear-cut symptoms resulting from pyridoxine deficiency have been described in human beings, but additional improvement in pellagra, beyond that brought about by nicotinic acid riboflavin and thiamine, was believed to follow its use (Spies et al.: J 11 : 414 1939) Cheilitis was reported as being promptly responsive (Smith and Martin: PSExperBiol 43: 660 1940) It has been tried by topical application in seborrheic dermatitis (q.v)

See Dann and Subbarow (JNutrit 16 183, 1938) Harris and Folkers (Sci 89: 347 1939) chemical synthesis Edit (J 113 482, 1939) chemistry Council on Pharmacy (J 147 321, 1951)

Biotin (Vitamin H) (du Vigneaud et al.: Sci 92: 62, 1940; György et al.: Sci 92: 609, 1940) is a growth factor needed by many bacteria and molds and most animal (Edit: BMJ 2: 655 1945) Deficiency is produced by adding raw egg white to the diet which inactivates it, or by feeding sulfonamides, which interfere with the bacterial synthesis of it. Thinning of fur in monkeys alopecia and scaly dermatitis especially of the face and extremities, were produced by withholding the nutrient by Waisman et al. (JNutrit 29: 1 1945) Human volunteers on a diet free from biotin poor in all vitamins except riboflavin and rich in egg white developed a fine scaly, nonpruritic dermatitis within a month under the observation of Sydenstricker et al. (J 118: 1199 1942) They also manifested reticulation of the extremities, depression, lassitude, anorexia, muscle pains and hyperesthesias. The syndrome was curable by the administration of 150 to 300 μg of biotin daily The requirement is hard to establish, for a large part of it may be supplied by the intestinal bacteria (Elvehjem: J 138 960 1948)

Choline is a component of the phospholipid lecithin and plays a role in the prevention of fatty livers in depancreatized dogs (Elvehjem J 120: 1388 1942) Considered an important member of the B complex its function is in some way related to the mobilization of fatty acids in the body serving perhaps to stimulate the formation of phospholipids, to make possible the production of acetylcholine or to supply labile methyl groups as

methionine does (McHenry Choline the B Vitamins and Fat Metabolism Lancaster Pa, 1941) Experimental animals deprived of choline showed marked deposition of lipids in the liver (NutritRev 5 116 1947) In supporting the function of a subnormal liver benefit may accrue from giving choline along with the usual adequate-protein, high-carbohydrate diet (Burns RhodeIslMJ 30 729 1947) Its utility in dermatology is as yet unassessed though it has been tried in xanthoma and psoriasis.

Inositol, related in chemical structure to d-glucose, a crystalline powder of sweet taste, was shown by Woolley (Sci 9?: 384 1940) to be the factor responsible for cure of deficiency alopecia in mice It has a lipotropic action complementary to choline in avitaminotic rats (MacFarland and McHenry JBiolChem 139 176, 1948) which has also been observed in human beings (Abels et al.: PSExperBiol 54: 157 1943) It possibly has, in conjunction with choline the ability to enhance hepatic function when the liver is fatty

Folic Acid has been proved to be the *Lactobacillus casei* factor pertinent in primary macrocytic anemia, and its administration in the crystalline form induces prompt increase in red blood cells, reticulocytes, and hemoglobin in such cases (Spies et al. SouthMJ 38: 707 1945) Parenteral and oral administrations are equally effective in nutritional pernicious anemia and the macrocytic anemia of pellagra in a dose of 5 to 10 mg by injection or 100 mg by mouth daily (Spies J 130: 474 1946) Lopez et al. (J 132: 906, 1946) rehabilitated patients with sprue satisfactorily although the intestinal parasites were not altered.

The failure of folic acid alone to prevent the neurologic sequelae of pernicious anemia was learned early A case of pernicious anemia placed on folic acid showed response in the blood picture, but serious neurologic relapse occurred despite the vitamin (Heinle and Welsh: J 133: 739 1947); see Vilter et al. (JLabClinM 3?: 762 1947) Hall and Watkins (JLabClinM 3_ 622, 1947); Sargent (NEngJM 237: 703 194) Liver therapy is necessary too (Haden and Bortz: J 138 870 1948) Not all macrocytic anemias respond to folic acid, but favorable response may be expected in cases characterized by megaloblastic arrest in the bone marrow (Adams and Lawrence: AmJMedSci 15: 487 1948) It is of no benefit to persons with normoblastic marrow (Wilkinson BMJ 1 771 1948) Its value is in the therapy of pernicious anemia macrocytic anemia of pregnancy and of infancy pellagra sprue steatorrhea, celiac disease and nutritional macrocytic anemias. Its administration promotes the enteral absorption of iron (Bergemann et al.: KlinWchn 31: 881, 1953)

Folic acid is a pteroyl acid ester containing para aminobenzoic acid and 1 molecule of glutamic acid (Edit: J 146: 733 1951) first synthesized by Angier et al. (Sci 103: 667 1946)

Folic acid antagonists may be used in treatment of leukemia (q v) to prevent the luxuriance of white blood cell growth.

Cyanocobalamin (Vitamin B) is a factor required by *L lactis* and present in refined liver extracts in close parallel with the antipernicious anemia potency of the extract (Shorb JBiolChem 169 455 1947) Crystallized (Rickes et al Sci 107 396 1948) it produced hematologic response in 3 cases of pernicious anemia when given in single intramuscular doses of 36 to 150 micrograms (West Sci 107 398 1948) One microgram is approximately equivalent to one U S P unit of extract of liver or stomach mucosa (Hall and Campbell PSMBIC 23 584 1948) Spies et al. (SouthMJ 41 522, 1948) confirmed its value in Addisonian anemia and sprue with striking clinical improvement including an increase in feeling of well being mental alertness strength vigor and complete relief of soreness and burning of the mouth and tongue.

B improves the neurologic condition of a patient with pernicious anemia whose neuritis has progressed while under treatment with folic acid alone reported Berk et al (NEngJM 239 328 1948) Alone, B is ineffective when given orally but the combination of gastric juice plus B_1 is followed by hematopoietic response (Hall et al. PSMBIC 24 99 1949) It is the most potent antianemic factor known (Spies et al. J 139 521 1949)

It is being used by dermatologists, especially in the treatment of lichen chronicus simplex (q v) lupus erythematosus (q v) and glossitis suggestive of vitamin deficiency Large doses should be given at the beginning of treatment to replenish depleted tissue reserves (Mollin and Ross BMJ 2 640 1953) IV doses of 1000 mg or more may be given safely (Goldblatt AmJ ClinNutrit 3 129 1955)

The intrin c factor of gastric juice, without which B_{12} given orally is ineffect al, is not needed for assimilation when B_{12} is given by injection (Edit: J 157 44, 1955)

Cyanocobalamin is a red crystalline compound whi h contains cobalt, phosphorus and nitrogen, but not sulfur (R ckes and Konlusy Sci 108: 134 1948) See Council on

Pharmacy (J 143: 134, 1950) Other forms of B_{12} have been identified, a and b being identical (Smith: BMJ 1: 151 1951), and c being as effective as a in the treatment of pernicious anemia (Ungley and Campbell: BMJ 1: 15, 1951) See Edit (J 153 960, 1953) regarding B_{12} research.

B_{12} tagged with Co^{60} was used to investigate the metabolism of the vitamin by Callender et al. (BMJ 1: 10 1954) Normal individuals excreted 30% of it by way of the feces. Pernicious anemia cases excreted 89% of it, but if "intrinsic factor" was given also to the pernicious anemia cases, the fecal loss was greatly reduced. The intrinsic factor used was Factor B of hog stomach prepared by the method of Prusoff et al. (abs 118th meeting AmChemSoc 1950)

B_{12} may play an important role in the synthesis of nucleic acid, and growth studies emphasize its importance in the metabolism of carbohydrates and fats (Harte and Chow Sci 118 582, 1953)

Vitamin C (Cevitamic Acid)—The purpuric lesions of scurvy are due to capillary fragility and the tourniquet test shows that fragility is most marked in the perifollicular vessels. Swollen gums, loose teeth and gingival hemorrhages are typical features. In severe scurvy bloody tumors of the conjunctiva and ecchymoses of the lids and elsewhere about the eyes may appear but degeneration of the cornea, pigmentation and night blindness, once reported due to avitaminosis C are known to result from lack of vitamin A (Dalldorf J 111 1376 1938) Perifollicular or petechial hemorrhages characteristic of scurvy are commonest on the lower extremities, where hydrostatic pressure exposes the weakness of the capillaries. Follicular lesions resembling those of avitaminosis A may occur in scurvy (Scheer and Keil ADS 30 177 1934; György AJDnS 175 707 1937) Skin lesions, late to appear in an experiment reported by Fox (BMJ 1 311, 1941) were first manifested by small perifollicular hyperkeratoses over the buttocks and posterior aspect of the calves. The patient did not develop petechiae until the 161st day and there was no demonstrable increase in capillary fragility, but he lost 23 pounds in weight and showed follicular hyperkeratosis of the buttocks and calves and ascorbic acid given intravenously was promptly restorative (Crandon et al. NEngJM 223 353 1940) see Lund and Crandon (J 116 663 1941)

Inadequacy of vitamin C in infants is more likely to be manifested by pain in the lower extremities, irritability and edema than by bleeding gums, to be diagnosed by clinical and roentgenologic findings, stated Coward (CanadMAJ 63 549 1950) Bleeding of the gums does not occur in scorbutic infants until after dentition (Jeghers: NEngJM 228 710 1943) Barlow's disease (scurvy in infants) differs from avitaminosis C in adults largely because of differences in anatomy and physiology limb tenderness in the affected infant being the most constant positive finding and x ray diagnosis surest, for the patients look as if they were well nourished (Howells et al. BMJ 2 1143 1954)

The vitamin C concentration of the blood is related to the dietary intake, but apparently good health may be associated with low values, according to Lever and Talbott (ADS 41 657 1940) who could detect no relation to the vitamin in psoriasis, urticaria lupus vulgaris, lupus erythematosus, eczemas or purpura Scurvy affecting a family of 6 and caused by their peculiarly restricted diet was observed by McGovern et al. (AmJMedSci 197: 310 1939) As judged by blood levels of ascorbic acid, some 5% of private patients seen in Boston in 1953 were prescorbutic or frankly scorbutic reported Morris (AmPract 5: 658 1954)

Saturation may be estimated by determinations of urinary excretion of ascorbic acid after giving 600 mg intravenously (Goldsmith and Ellinger: AIntM 63 531 1939) Wound healing well-being and complement titer are probably significantly related to adequacy of the vitamin C level (Ecker et al. J 112 1449 1939) yet the utility of its administration in dermatology lacking such classic indications of its need as were described by Osterlin (JMichSMS 44 1351 1945) in scorbutic children is quite dubious. It may be given intravenously in large doses and may diminish reactivity to arsenicals (Cormia JID 4 81 1941) See Council on Pharmacy (J 142 563 1950)

Aural Lesions were reviewed by Burgess (TexasSJM 43 283 1947) who corroborated Ruskin s report that C-deficiency is related to bullous, hemorrhagic myringitis.



Fig [illegible].—Avitaminosis C gingival swelling which almost completely obscures the teeth and petechiae. (Dr R. Staehelin.)

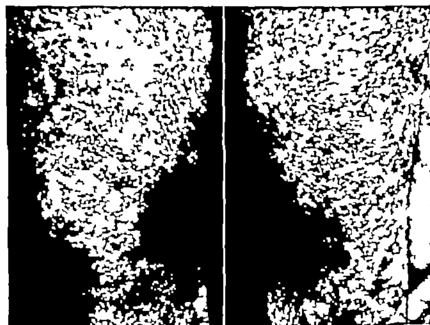


Fig. [illegible]—Avitaminosis C follicular petechiae. (Dr R. Staehelin.)

Oral Changes in Avitaminosis C—The teeth of adults, Dalldorf (1938) noted, are damaged by resorption and porosity of the dentine and the replacement dentine which forms is defective. In the pulp chiefly about the vessels, occurred atrophy hyperemia degeneration of the odontoblasts and the formation of small cysts and foci of calcification. The lesions develop

first in the apex of the tooth and in the bifurcation of the root canal. The fluid ground substance noted in experimental scurvy has also been observed in human material. Defects in the enamel and cementum of guinea pigs have been demonstrated by Fish and Harris (BritDentJ 58: 3 1935) Lesions of the gingivae occur only when teeth are present, Dalldorf continued. They are most severe about deformed or broken teeth. The gums become swollen and boggy and they bleed easily They may swell so much that they hide the teeth and make mastication painful and difficult. Rarefaction of the alveolar bones results in loosening of the teeth. The gingival lesions begin on the papillae, first as hyperemia with dilated, thin walled vessels and a tendency to intractable bleeding Disintegration of the epithelium, infection, ulceration, granulations, even gangrene follow Lesions of the mouth are remarkably constant manifestations of scurvy

The Physiologic Function of vitamin C is concerned with oxidation reduction phenomena, and its action in relation with complement in immunology is likewise probably of this nature (King J 111 1098 1938) Rutin appeared to Crampton and Lloyd (Sci 110 18 1949) to enhance the biologic potency of vitamin C

A Skin Test for determining the status of the supply of vitamin C was suggested by Rotter (Nature 139 717 1937) As modified by Portnoy and Wilkinson (BMJ 1 328 1938), this is performed by injecting intradermally 0 01 cc. of a solution of 2 mg 2,6-dichlorphenolindophenol in 4.9 cc. of water The color fades at a rate suggestive but not accurately mensurative of the quantity of vitamin C in the tissues 5 minutes indicate normal 10 minutes, delayed. See Slobody et al. (JPediat 28: 134 1946) The test is of doubtful value (Wright and MacLenathan JLabClinM 24 806 1939)

Vitamin C and Pigmentation —Cornbleet (ADS 35 471 1937) found that pigmentation in the skin increases when vitamin C depots are depleted and that the pigment seems to anchor the vitamin in the skin. Lack of vitamin C accelerates the production of pigment and pigmentation due to avitaminoses appears especially on the exposed parts (Hoff DMedWchn 62 129 1936) It is on this account, perhaps, that eating lemons has been recommended to cultivate a pretty complexion. That depigmentation may follow the use of massive doses of cevitamic acid in Addison s disease was confirmed by Abt and Farmer (J 111 1555 1938) in their thorough review of the pharmacology of the agent.

Hesperidin and Eriodictin (Vitamin P) —Vitamin P (Citrin) has been found to consist of 2 flavone components, hesperidin and eriodictin. It appeared to be concerned with the regul tion of capillary permeability and fragility (Wawra and Webb: Sci 96: 302, 1942) and corrected fragility in scurvy cases in which ascorbic cid alone complished only partial cures (Scarborough: Lancet 2: 644 1940; EdinMJ 50: 85, 1943) The Sze t Györgyi preparation proved inert, howe er when purified and the hemorrhage-preventi e may ctually be rutin (Edit: BMJ 1: 771, 1947) See purpura; Goldm n and Corrill (JID 6 129 1045) The name, vitamin P should be discontinued (Sci 112 628, 1050)

Vitamin D —Cod liver oil is a rich source of the antirachitic vitamin. I have seen epidemics of acne caused by its wholesale administration to groups of children. The effect of the oil in the etiology of acne (q v) is due I presume to malmetabolism of provitamin A. Vitamin D concentrates, such as Ertron and calciferol, have utility in the treatment of lupus vulgaris (p 338) and perhaps psoriasis (Wright ADS 43: 145 1941)

The lack of vitamin D does not produce cutaneous symptoms. Over dosage with vitamin D is toxic (see Dermatitis medicamentosa; also Lupus vulgaris, treatment) The use of D in various dermatoses was reviewed by Strakosch (ADS 67 496 1953) who thought it helpful in atopic dermatitis.

Vitamin E, of which wheat germ oil is a rich source is essential to the successful completion of pregnancy and to lactation (Mattill J 110 1831 1938) Without it the male testis becomes sterile The tocopherols are crystalline substances of potent vitamin E activity (Evans et al. JBiolChem 113 319 1936 Sci 88 38 1938) Alpha tocopherol was synthesized by Karrer et al. (HelvChimActa 21 520 1938) a plausible dose is 100 mg per day but

no harm has come of much larger doses, although an occasional idiosyncrasy such as pruritus or urticaria has been reported (Shute AmJObG 35 249 1938) The tocopherols may be useful in some cases of pruritus vulvae, being perhaps antagonistic to estrogen. Necrobiosis lipoidica responded favorably as did several cases of lupus erythematosus and of sclerotic leg ulcer reported by Burgess (Lancet 2 215 1948) and Burgess and Pritchard (CanadMAJ 59 242, 1948 ADS 57 605; 953, 1948) They pointed out the influence of vitamin E on fat metabolism and collagenous tissues, and indicated its possible utility in poikiloderma arthritis, Dupuytren's contracture and knuckle pads. The true usefulness of the tocopherols is still *sub judice* (see BMJ 1 951 1948) and is perhaps overestimated especially with regard to alleged virtue in heart disease (J 138 1159 1948)

Vitamin F comprising the unsaturated fatty acids linolenic linoleic and arachidonic necessary for the rat preventing scaly dermatitis (Edit J 11 2518 1939) is of unknown significance to the human being (Finnerud: ADS 44: 849 1941) See eczema, atopic also Hansen and Burr (J 13 855 1946)

Vitamin G is B_2, riboflavin (q v)

Vitamin H see Biotin.

Vitamin K is an antihemorrhagic factor which shortens a prolonged prothrombin time. *Richly present in alfalfa its isolation chemical constitution and synthesis were described* by Doisy et al. (Sci 90: 407 1939) see also Snell and B tt (J 113: 2056, 1939) It has been used successfully in some cases of purpura (q v) for in its deficiency ecchymoses and suffusions, especially over pressure sites, rather than dependent ones, may cover large areas of skin (Kark et al.: QJM 9: 47 1940) Vitamin K counteracts the overdosage effect of Dicumarol. See Council on Pharmacy (J 143: 236 1950)

Vitamin L, obtained from liver extract more recently from an Egyptian herb, is a lactation factor for rats, similar to the filtrate factor W and is of dubious status (Edit BMJ 196 1940 181 1947)

Vitamin M is a dubious member of the B complex in liver extract Its deficiency in the monkey produced glossitis and symptoms of sprue (Day et al. PSExperBiol. 38: 860, 1938) and was restored by injections of purified *L. casei* facto (Darby et al.: Sci 103: 108, 1946) so that it probably actually is folic acid.

Treatment of the Avitaminoses is direct and satisfactory It is better to err on the side of excessive dosage for ill effects from moderately large doses are unusual Many of the avitaminotic patients one sees are persons of limited economic means and understanding but capable of being taught to spend a meager food allowance more to their profit Appropriate vitamin therapy may be depended on to relieve avitaminosis it is no panacea. Hydrochloric acid is generally advisable if the B complex is to be prescribed (Allison SouthMJ 38 235 1945) Hyperthyroid patients are as a class deficient in the B complex (Goldsmith SouthMJ 36 108 1943) Half of an orange a day promptly cures the scurvy I see in my dispensary work A pork chop is a rich source of vitamin B_1 Pellagra must be recognized and its efficient treatment is inexpensive and satisfactory Spoon nails and smooth tongue in an anemic, middle-aged woman with dry lusterless hair call for improvement of nutrition probably iron, and perhaps hormonal therapy

Malnourished persons need careful study They *should not* be given merely a prescription for a proprietary shotgun capsule despite the fact that these are carefully compounded and expertly designed by the drug houses, and despite the fact that as a rule if a person needs one vitamin he needs several. An adequate diet contains more of course than merely vitamins.

Practically all individuals who need vitamins also need correction and improvement of dietary habits. When economic problems interfere with adequate nourishment welfare and governmental agencies come into the problem and physicians when they concern themselves, are able to guide their patients and help them greatly It has been hard to see through the murk of faddism among alleged nutritional experts, but creditable investigators, of genius and persistency are clarifying the scientific problems, and science eventually reaches the public

See Youmans (J 108 15 1937) clinical summary of avitaminoses Goodman (ADS 35 389 1936) dermatologic symptoms, review Booth and Hansen (J Lancet 57 520 1937) history standardization, symptoms, requirements Harris (Vitamins and Vitamin Deficiencies,

Blakiston, 1938, 204 pp.) Nelson (J 110: 645 1938) B complex components, bibliography Lewis (Ann [illegible] 13: 749 1939) discovery review Maynard (ADS 41 842, 1940) vitamin therapy in dermatology; Sull and Nicholls (JID 3 309 317 337, 1940) review, Sulzberger and Cope (JLabClinM 26 1401, 1941), vitamin therapy, O'Leary (ADS 46 8-8, 1943) dermatologic uses Jeghers (NEngJM 228 678, 714 1943) review of A,B,C,K,P Callaway et al. (ADS 51 248, 1945) miscellaneous skin cases not different from regional public with respect to A Cornbleet et al (ADS 49 103, 1944) plasma A in skin cases, showing little abnormality Cayer (J 133: 888, 1946) food sources, Assn of Vitamin Chemists (Methods of Vitamin Assay Interscience Publishers, N Y 1947); Elvehjem and Krehl (J 135 279 1947) dietary imbalance and nutritional interrelationships; Keddie (ADS 58 64 1948), dermatologic uses of A; Follis (Pathology of Nutritional Disease, Thomas, 1948) monograph Heerstecher (Sci 111: 300, 1950) comparative biochemistry of vitamin function Gilder (BMJ 1 441 1950), experimentally induced vitamin deficiencies in man Youmans (J 144 34, 307 386, 1950) deficiencies in fat-soluble A,D,E,K Lady (Vitaminology the Chemistry and Function of the Vitamins, London, 1950) Williams et al (The Biochemistry of B Vitamins, Reinhold, 1950), Robinson (The Vitamin B Complex, Wiley 1951) Sherman (Chemistry of Food and Nutrition, ed 8, Macmillan, 1952) Bicknell and Prescott (The Vitamins in Medicine, Grune and Stratton, ed. 3, 1953); Sebrell and Harris (The Vitamins Chemistry Physiology Pathology 3 volumes, Academic Press, 1954) comprehensive review



Fig. 364.—Pellagra an acute, severe case with extensive dermatitis of parts exposed to the sun (Drs. M. C. Stone and O. L. Castle.)

PELLAGRA

Symptoms.—This avitaminotic symptom complex represents deficiency in the B factors particularly nicotinic acid. Degrees of severity are widely divergent the classic epitome of the extreme case being given by the four D s, dermatitis, dementia, diarrhea and death. Since several vitamins rather than one are usually simultaneously deficient and the relative inadequacies of each may be different and the causes of deficiency may differ the variety of manifestations embraced by the connotation of pellagra is considerable. Typical symptoms include gastrointestinal and neurologic disturbances accompanied by dermatitis pigmentation, and photosensitivity

Cutaneous lesions generally affect the dorsa of the hands, wrists and feet and the face and neck. The eruption is generally symmetric. Early changes are large, inflammatory macules which coalesce to form patches resembling sunburn. There is more or less pigmentation in brunettes often being marked and when desquamation takes place a rough scaly surface results, from which pigmentation may be largely absent. In acute and severe examples, bullae may form. Lesions are likely to become secondarily infected. Sunlight influences the location of lesions. These may also be determined by stasis, scars, injuries, burns, friction and inflammation, and relapses may be induced by heat and ischemia (Bean et al. ADS 49: 335 1944) so that the eruption is not always symmetric Actual dermal atrophy is rare The cutaneous manifestations in pellagra are rarely serious in themselves, and are





Fig. 965.—Pellagra dermatitis of exposed skin. (Drs. Harrington and T. Twyman.)
Fig. 966.—Pellagra. (Dr. O. L. Castl)

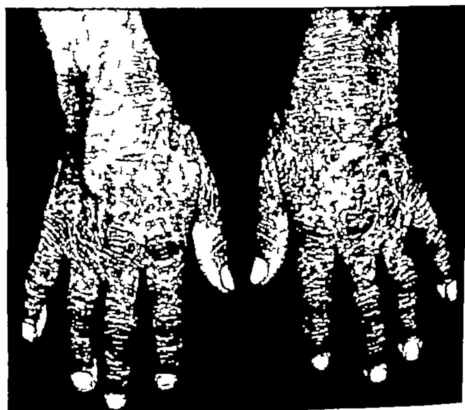


Fig. 96 .—Pellagra dermatitis and pigmentation of backs of hands. (Dr Grover W Wende.)

of little value in prognosis, but in diagnosis they are invaluable Because of the ill-defined character of the symptoms arising from gastrointestinal and nervous involvement many pellagrins would go unrecognized if it were not for their skin lesions, which are typical and distinctive. Bloom (AmMed 23 331 1928) emphasized their diagnostic value in children with the disease

Symptoms referable to the gastrointestinal tract are generally present, but range widely in severity The tongue is usually swollen dry and denuded, and both it and the buccal mucosa may present yellowish superficial sloughs. In mild cases, the tongue may be redder and smoother than normal particularly at the tip the bald tongue of Sandwith

Cheilitis and stomatitis are expected, and colpitis and vulvar dermatitis are common. Monilial infection of such subnormal mucosae is usual the monilia disappearing when nutritional therapy is adequate. Diarrhea is commonly but not invariably present. There may be constipation or constipation alternating with diarrhea. The stools have often a peculiar foul odor and may contain mucus and partially digested food. Emaciation and weakness correspond in the main with the severity of gastrointestinal symptoms. Vaginitis and proctitis correspond in severity with stomatitis.



Fig. 148.—Pellagra, showing "Casal's collar" in a Mexican woman with extensive lesions elsewhere. (Dr Robert N Andrade)

Fig. 149.—Pellagra, showing involvement of feet. (Dr C. H. Lavinder U S. Public Health Service)

Anemia diminished blood protein and dependent edema may occur

Neurologic manifestations include toxic psychosis, confusional or even maniacal and polyneuritis, loss of reflexes and paresthesias. The psychotic symptoms are similar to those occurring in various toxic states. Chronic toxic psychosis may be a sole symptom, curable with nicotinic acid (Evans J 112 1249 1939) Retrobulbar neuritis preceded the development of frank pellagrous symptoms in 3 cases reported by Fine and Lachman (AmJOphth 20 708 1937) Peripheral nerve lesions were discernible in three-quarters of the patients of Lewy et al (AmJMedSci 199; 840 1940)

Exposure to sunlight may precipitate pellagrous dermatitis in susceptible subjects (Smith and Ruffin AIntM 59 631 1937 McFadzean GlasgowMJ 28 103, 1947) Acute onset may be manifested by confusion and sore tongue (Gottlieb BMJ 1 392 1944), and the postoperative period especially after gastrointestinal surgery may be the occasion of the appearance of pellagra. Psychoses of the senile type, with memory defects and episodes of stupor accompanied by mucosal changes of avitaminosis, are sometimes attributable

to pellagra (Meyersburg NEngJM 233 173 1945) Infants and children also suffer from nicotinic acid deficiency in areas where pellagra is endemic, although typical lesions are seldom seen in infancy (Spies et al. J 113 1481 1939) The dietary histories of the mother and infant and the response to the administration of specific therapeutic agents make the diagnosis.

Atypical cases have been described by Smith et al. (JID 41 23, 1941) wherein "dyssebacia" is seen with dry flakiness of the face and plugged sebaceous follicles, features now recognized as mainly due to ariboflavinosis or hyperkeratosis over the pressure sites, ichthyosiform alterations, swelling of the tongue paresthesias and loss of energy may comprise the picture (Field et al.: NEngJM 223: 30 1940) Nondescript stomatitis and glossitis in patients in a mental hospital were actually pellagrous reported Evans (BMJ 2 458, 1939) Unusual location of the dermatitis, such as submammary and vulvar interested Riordan et al. (ADS 46: 001 194)

Purpura linear in configuration, resulting from scratching and not related to vitamin C deficiency sometimes is a symptom of pellagra (Simons and Simons: BMJ 2: 817 1946)

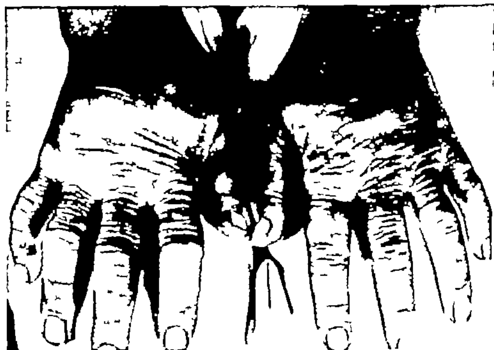


Fig 910—Acute bullous dermatitis following sun exposure in pellagra (Dr Sam E Sweitzer)

Diagnostic problems, atypical and borderline cases, were discussed by Gross (ADS 43: 504 1941) and Spies et al. (J 126 75.., 1944) X ray examination of the gastrointestinal tract may reveal dilation and slow emptying of the stomach, atrophy of the mucosa and gas in the gut (Rubro and Holda : also J 121 86 1943) The electrocardiogram may show sinus tachycardia, alteration of the ST interval and of the T wave and low voltage but no characteristic feature (Mainzer and Krause BritHeartJ 83 1940)

The course of the chronic disease is variable It generally becomes manifest in the summer or early fall, lasting a month or more Dermal symptoms may recur during several successive summers. Neurologic changes are seldom demonstrable in mild cases but sometimes comprise the conspicuous or even the sole findings. Mental symptoms and peripheral neuritis are attributable to the lack of B

Etiology and Pathology—No age or class of persons is exempt although elderly people of poor economic status are the usual victims. The endemic regions in the U.S.A. are characterized by a population with a high proportion of persons whose economic circumstances are substandard and whose diet includes a good deal of maize of which the nicotinic acid content is so low that the daily requirement could be met only by eating two pounds a

day (Elvehjem J 138 960 1948) But pellagra occurs in anyone in whom the ingestion, absorption or utilization of the essential nutrient factors is inadequate (O'Leary NoWMed 27 319 1928) The alcoholic senile or mentally defective individual failing to nourish himself decently is subject to pellagra. Anatomic interference with gastrointestinal function and absorption may be causative Intestinal parasites or other debilitating circumstances may tip the balance unfavorably when the supply of the required vitamin is borderline.

In one family th members of whom were on the same diet, some were pellagrous a l others not; and in those with pellagra a Cairo physician (quoted l y Spies et al.: J 111: 584, 1938) discovered heavy gastrol testinal infestation with parasites. Their pellagra could be cured by curing the parasitism without altering the diet. Pellagra occurred in wealthy person who were similarly infested with *Schistosoma mansoni* or *Ancylostoma*.

That dietary inadequacy is an essential factor was strongly indicated by the experiments of Goldberger and Tanner (J 79: 2132, 1922) who believed that diet controls the cause and development of the disease depending on specific quality of the amino acid make-up of the protein supply Th studies by Goldberger et al. (USPHS HygLabBull No. 153, 1928) indicated that blacktongue in dogs and pellagra in man are of the same nature Pijper (SoAfrMJ 17: 248 1922) reported interesting observations on the occurrence of pellagra in South African natives, who subsisted almost entirely upon mealies and mealie meal, despite which the disease is practically unknown, Pijper having been able to discover only cases in the course of many years. Culver (BMJ 2: 751 1929) made similar observations i South Africa. Searcy in 1907 (quoted by Carmichael: J 114: 678, 1940) knew that good diet was curative among the Tennessee Negroes. Boldchaux (JAMA 23: 6, 1925) and Klauder and Winkelman (J 90: 364 1928) are among those who have shown that chronic alcoholism is an important predisposing factor Looml told me in 1933 th t of 103 cases i the Cleveland City Hospital since 1924, 89 case records included statements as to alcoholism. Of these 94 4% admitted alcoholism, and 5 6% denied it. Beverages consumed included whisky corn raisin jack, denatured alcohol and Brilliantine Th death rate was 33%. Sweitzer (MinnM 11: 719, 1928) emphasized th important relationship between chronic alcoholism and pellagra, and Winkelman stated that all chronic alcoholics are potential pellagrins. The loss of appetite i chronic alcoholism is highly significant, believed G thrie (NEngJM 201: 414, 1929)

Sutton (AmJMedSc 172: 374 1926) studying 56 cases from the May Clinic, separated them into 3 types: early cases in which symptoms and findings were trivial; late cases, in which the symptoms were severe and cases in which the complications overshadowed the symptoms of pellagra. He concluded: Pellagra is probably not a simple deficiency disease like beriberi and scurvy While the causative agent is not known, it is probably of an infectious nature and gives rise t some substance which sensitizes the patient t sunlight and ambulatory patients d better outside the hospital than when rigidly hospitalized H called attention to the necropsy findings, which are trivial for so serious a disease and to the importance of the skin lesions as diagnostic factors.

O'Leary (1928) classified cases of pellagra in 6 gro ps: idiopathic (dietetic deficiency not demonstrable); dietetic; anatomic interference with the intestinal tract alcohol type; pellagra in insane; pellagra without kin symptoms. He noted that pellagrins serums show high toxicity in the Pels-Macht test (q.v.) The blood f pellagrins supports the growth of *B i fluenza* badly as compared with normal blood; after giving nicotinic acid, pellagrins' blood becomes like normal in this regard (V lter et al. J 112 420, 1939) Scott (NOrlM&SJ 90: 403, 1938) described 14 cases due to lesions of the gastrointestinal tract; of these, 7 were due t rectal stricture from lymphogranulomatosis inguinalis. Mackie (J 104 1 6, 1935) observed evidences of deficiency states in the majority of 75 cases of ulcerative col tis; inflammation f lingual papillae aphthous ulceration, atrophy of the tongue dry scaly skin, follicular hyperkeratosis, pigmentation and erythematous eruptions were among the symptoms noted. DeKleine (AmJPubH 27 595 1937 SouthMJ 35: 992, 194.) concerned with the incidence of the condition, found pellagra a poo ma 's disease, and mainly rural problem: bad food habits re commonly involved, especially the failure to ingest milk, lean meat a d vegetables. Diet ry idiosyncrasies and eccentricities, food fad and obsessions, alcoholism and disease of the gastrointestinal tract account f those cases which re ot due to simple poverty according t Garrett (AmJMedSci 190: 525, 1935) After st dying 403 cases, Flinker (Wie MWchs 84: 900 930 960 1934) insisted that pellagra may occur despite a well-assorted dietary that persons free from the disease for years develop t duri g a period when no change in diet is made, and that the disease is comparable w th pernicious anemia i it remissions and int rmissions.

Obt ini g improvement by the admi istr tion of gastric juice, S) denstricke et l (AmJMedSci 191 1, 1936) postulated a d ficiency of a i trinsic factor which enables the utilization f B, analogous to that which influences absorption in pernicious anemia. Petri et al. (ActaMScand 93: 450 1937) cured cases with Ventriculin and hydrochloric cid. They observed that pellagra has been known to occur in individ als with normal organs and on non deficient diets, that aggravation may occur during a time when yeast is being fed to the

patient, that remissions occur despite the continuance of pellagra producing diet, and that, therefore mere B_1 deficiency does not account for the disease They believed that a double factor must be involved, as did Goldberger et al. (J 1: 844 1918) Wilbur (AIntM 61 340, 1938) suggested that 4 factors may be involved: riboflavin, the rat antidermatitis factor B_6, the filtrate factor of chick dermatitis, and the pellagra preventive (P P) factor Sunlight he believed, serves merely to irritate and so to precipitate the acute manifestations.

Specific Pellagra Preventive Factor.—Chittenden and Underhill (AmJ Physiol 44 13 1917) found that diets like those of pellagrins caused black tongue in dogs. Red meat and yeast prevented and cured both pellagra and the Goldberger type of blacktongue which must therefore be the true analogue of human pellagra. *Goldberger et al. (PHRpts 40 927 1925)* showed that dried brewer s yeast benefits human pellagra and canine blacktongue in as short a time as 2 or 3 days.

While Funk (J 109 2086 1937) had isolated nicotinic acid in 1911 (JPhysiol 43 395) while trying to isolate vitamin B from yeast and rice he found it inactive in curing polyneuritis in pigeons and investigated it no



Fig. 871 —Histology of pellagra, showing superficial inflammation, epidermal atrophy and irregular hyperkeratosis. (Moore et al. ADS 46 100, 1942.)

further It was Elvehjem and Madden (Sci 86 12, 1937) who observed that crystalline nicotinic acid amide cures blacktongue in dogs. Ruffin and Smith (AmJMedSci 187 512, 1934) showed that, on a diet complete but for the B_2 complex, the skin lesions disappeared but could be reproduced by exposure to sunlight the giving of liver extract then induced prompt recovery Elvehjem et al. (JAmChemSoc 59 1767 1937) obtained their nicotinic acid amide from a liver concentrate which was active in curing blacktongue They found that 30 mg cured one dog and that, if given in a diet that normally causes the disease, it prevented the development of the disease. *It was Smith* et al. (J 109 2054 2086 1937) who cured one human pellagrin whose diet throughout the whole study was deficient in the preventive factor the only treatment being 60 mg nicotinic acid daily given into the muscles with additional amounts orally and intravenously to a total of 720 mg in 12 days. Dramatic improvement began at once and cure was said to have been complete in the 12 days.

It had been predicted (Edit J 109 1203 1937) that nicotinic acid having been found curative of canine blacktongue, would prove useful in human

pellagra; further (J 110 289 1115 1938) it was predicted that while nicotinic acid would cure the glossitis, it would not relieve the neuritis, for thiamin chloride, crystalline vitamin B_1 hydrochloride, given intravenously does relieve neuritic pain. Spies et al. (J 110 622 1938) found these opinions borne out by experience: 11 patients treated with nicotinic acid were cured of glossitis, stomatitis colpitis urethritis and proctitis and these symptoms did not reappear during treatment with nicotinic acid although the diet remained pellagra producing They found that 100 mg given by mouth 5 times a day is safe and effective It could be given intravenously in doses of 50 to 100 mg daily but must be given slowly to avoid severe vasodilatory reaction.

Nicotinic acid is 3 pyridine carboxylic acid; see Elvehjem (PhysiolRev 20: 249 1940)

Lack of B_1 causes the neuritic symptoms, but to give it does not cure stomatitis, while nicotinic acid does not help neuritis but does cure mucosal inflammation (Spies and Aring: J 110: 1081 1938)

Among patients whose pellagra recurred annually Spies et al. (SouthMJ 31: 1231 1938) undertook prevention by supplying them with nicotinic acid at weekly visits to the clinic, without altering the diet. As the season advanced, it usually became necessary to increase the initial dose. Infections, strenuous exertion, or extremely defective diet tended to necessitate increase in dosage In almost every patient medication was followed by increase in the sense of well being and vigor; indigestion nausea and diarrhea were relieved. Some developed polyneuritis, but clinically active pellagra did not appear: deprived of nicotinic acid, however the patients suffered recurrence of their symptoms within a week. None died of uncomplicated pellagra.

Patients with acute pellagra are well treated, they determined, by nicotinic acid in doses of 50 milligrams given 10 times a day by mouth, even if vomiting occurs. A liberal and well-balanced diet must be urged. The fiery redness and swelling of the tongue disappear within 24 hours f the commencement of specific therapy salivation and oral discomfort promptly diminish, and Vincent's infection heals quickly Erythematous skin lesions blanched rapidly, but nicotinic acid seemed to have less effect when the lesions were moist, ulcerative, dry or pigmented. Nicotinic acid is not a substitute for a full balanced diet.

Niacin (nicotinic cid amide) intake is not the whole story in pellagra. The intesti nal flora in man produce and release nicotinamide in consequential amounts; the signifi cance of this is discussed by Ellinger (J 130: 668, 1946) Krehl et al. (Sci 101: 489 1945) showed that tryptophane prevents deleterious effects f corn in the di t, it being previously known that corn ingestion increases th niacin requirement (Edit: J 129: 73, 874 1945) Overingestion of adenine prod ces pellagra in dogs, and a relationship exists between purine metabolism and avitaminosis according to Raska (Sci 105: 126, 1947)

An extract of the liver of a pellagrin who died effected blood regeneration in a patient with pernicious anemia but did not benefit other pellagrins, whose subsequent response to commercial liver extract was favorable (Sydenstricker et al: AmJMedSci 197: 755 1939) The pellagrin manifests abnormal sensitivity to insulin, as does the sufferer from Addison's disease, respondi g to small doses with deep and prolonged hypoglycemia (Malzer: abs J 113: 980 1939)

Pathology.—The blood and urine show nothing distinctive (Spies and Chinn JClinInv 14 941 1935) There are no qualitative changes in the white count. The post mortem findings are those of a generalized intoxication. There are fatty degeneration of the liver and inflammation of the intestinal mucosa but nothing of a specific nature has been found either in this region or in the nervous system (Spies and Armstrong: AIntM 59 883 1937)

Cutaneous changes in pellagra are dyskeratotic and inflammatory, but nonspecific, and are reversible under appropriate treatment (Moore et al.: ADS 46 100 1942)

The peripheral nerves show swelling and defibrillation of the fibers, a secondary toxic degeneration such as lead poisoning produces (Rosentoul ActaD-V 15 495 1934) The cerebrospinal fluid shows no change Campbell (AmJMedSci 186 266 1933) found that pellagrous blood regularly reduces and decolorizes iodine solution faster than normal he made this the basis of a test which, if positive suggests the presence of the disease.

PHOTOSENSITIZATION.—The excretion of porphyrins by pellagrins is generally greater than n rmal, and it is roughl related to the severity of the dermatitis present (see also Hydroa) While Jobl ng and Arn ld (J 80: 365, 1923) were able to culture a fungus from

the feces of pellagrins which yields a substance capable of producing photodynamic sensitization in mice Mathews (AIPath 23: 411 1937) believed that photodynamic sensitization in pellagra is secondary a result rather than a cause.

Porphyrinuria is not constant in pellagra, nor does its severity parallel that of the symptoms (Spies et al.: SouthMJ 31 483 1938) and it is not the explanation of the photosensitivity (Kark and Meiklejohn: AmJMedSci 201 380 1941) When present, it depends perhaps on altered hepatic function, and the administration of nicotinic acid in curing all symptoms of the disease is followed also by return of the urine to normal.

Diagnosis.—The disorder might be confused with certain forms of dermatitis, erythema multiforme and photodynamic sensitization.

The picture is not always characteristic. As Haden (J 106 261, 1936) pointed out It is better to consider clinical deficiency symptoms as deficiency disease than deficiency diseases. The occurrence of dermatitis and pigmentation together with stomatitis and glossitis, suggests deficiency of B_2. He described cases illustrative of the overlapping of deficiency syndromes, such as pellagra with pernicious anemia and pellagra with scurvy Cure he showed depends upon the needed factors being *supplied absorbed* and *utilized* in adequate quantity and error at any of these points spells trouble. Variation in degrees of deficiency exists, and combinations of deficiency states are common. See Spies and Cooper (InternatClin 4 1 1937)

Prognosis.—The outlook is in part dependent on the condition of the patient when the disease is recognized and treatment is begun. The acute severe cases were likely to prove fatal and severe gastrointestinal and neuritic involvements were of bad omen Of 2o8 cases reported from the Peoria State Hospital by Siler and Nichols (MRec 77 87 1910) half died. Such mortality would not obtain with modern methods of attacking the disease. Reports during 1938 of the effectiveness of nicotinic acid, along with vitamin B medication are in comparison miraculous. Intensive and intelligent treatment has vastly diminished the gravity of the disease Neglected advanced and moribund patients die Rutledge and Kelly (ADS 23 1072, 1931) reported epithelioma secondary to pellagrous dermatitis.

Treatment.—Patients with acute pellagra are well treated by nicotinic acid in doses of 100 mg given 3 times a day by mouth, even if vomiting occurs. The fiery redness and swelling of the tongue fade within 24 hours of the commencement of specific therapy salivation and oral discomfort promptly diminish, Vincent s infection heals quickly and erythematous skin lesions blanch rapidly Nicotinic acid is not a substitute for a full, balanced diet Nicotinamide does not cause the vasodilation that niacin does, and so may be given intravenously Adequate amounts of the whole B complex, and of protein also should be assured in any patient, for it is unlikely that niacin alone is deficient A liberal and well balanced diet must be urged

Patients with subclinical pellagra who were prone to have recurrences were relieved of recurrences when nicotinic acid was given, although some of them developed symptoms of deficiency of vitamin B_1 (Spies et al. 1938) Spies (J 104 1377 105 1028 1935) insisted that all cases which are properly treated do respond to treatment. Along with symptomatic measures, he prescribed a high-calorie diet and, daily 100 Gm yeast 200 Gm. Ventriculin, 300 Gm. wheat germ and 100 Gm. liver extract. Spies et al. (J 108 853, 1937) reported 50 cases with only 3 deaths, a therapeutic achievement of merit They used permanganate packs or baths for the dermatitis, opium for the diarrhea and pain, saline for dehydration a diet rich in yeast milk, raw eggs meat and suitable vegetables and they gave due credit to the value of careful and skillful nursing

Alcoholics with polyneuritis who were put on an adequate diet and given injections of liver extract and vitamin B concentrate were relieved of their polyneuritis even though they continued the use of alcohol (Strauss AmJMedSci 189 378 1935)

Hydrochloric acid, which is almost always deficient or even *absent* was advised by Sandorf (J 104 1845 1935)

Methionine seemed more effective and speedier than nicotinic acid in bringing about resolution and reversal of experimental blacktongue reported Caletti (Dermatologica 4 16 1953)

ACTH was given by Miowski and Tadzer (AnndeD 81 259 1954) who claimed noteworthy response

Prevention is of great importance. As Sebrell stated, generalities will not suffice, but the person must be given specific instruction to include amounts of green leafy vegetables, milk and lean meat in his diet. The encouragement of home gardening the free distribution of powdered yeast and the admixture of nicotinic acid with the salt for domestic use (Smith et al. J 109 2054, 1937) are measures which have been suggested

Education in self-sufficiency and self respect will serve in the long run, for the disease is, in the vast proportion of cases, caused by ignorance, *economic problems and personal inadequacies capable of being corrected* (Garrett AmJMedSci 190 525, 1935) Pellagra is being seen far less frequently than it was in 1930 perhaps because of the dietary reforms initiated by the Public Health Service (Blankenhorn J 140 1315 1949) Debilitating disease, including alcoholism is etiologic in more cases than poor diet.

STARVATION (WAR) EDEMA AND DERMATOSES ASSOCIATED WITH GROSS MALNUTRITION

Gross Malnutrition and Starvation, such as have occurred with distressing frequency among children of war torn regions and some prisoners of war result in a syndrome of emaciation, faintness, asthenia anemia bradycardia, hypotension paresthesias diarrhea and polyuria Cutaneous atrophy occurs, with wrinkling scaliness and pigmentation, especially of the hands, legs and face Mucosal involvement, including even ulceration, may develop resembling severe pellagra. Dependent edema appears in such persons suddenly Scabies, impetigo abscesses, ulcers and keratosis pilaris are common.

Jiménez et al. (abs J 122: 140 1943) reported such cases from Spanish civil war experience, and he found blood and plasma transfusions beneficial. Ortiz (abs J 115: 1979 1940) described similar findings in Puerto Rican children, whose diarrhea and general debility responded to high-protein diet, vitamins, iron and transfusions. Apathy and complaint of pain on passive motion a swaying gait in those who could manage to walk, and photophobia, alopecia and acrocyanosis were features of the starved Costa Rican infants described by Chavarria and Rotte (abs ADS 39 539, 1939)

Generalized edema, depigmentation of the hair photophobia and no descript dermatitis were features of the little patients of Bell (EAfrMJ 14: 327 1938) and they were helped by an antipellagra diet; see Kwashiorkor

Apathy and edema were features of children seen in Madras by Achar (BMJ 1: 701 1950); the patients exhibited "crazy pavement" or "mosaic skin" dermatosis, denudation of the epidermis flexural fissures, depigmented and hyperpigmented areas, pellagroid dermatitis, oral manifestations of malnutrition, dryness, brittleness and depigmentation of the hair, and diarrhea. Similar changes were seen in Nigerian children by Jelliff (BMJ 1: 1006, 1952), along with some cases of noma. The peeling of the hyperpigmented flakes in his cases with "raw" desquamation in contrast with the dry dermatitis of crazy pavement rash would leave a thin, pale weeping dermis, sometimes universal in distribution. The description resembles that of Brazilian "wildfire" pemphigus.

These syndromes and kwashiorkor probably represent variously combined features of inadequacy of protein, imbalance of amino acids and deficiencies of vitamin and mineral nutrition (Edit IJ IternatMDig 62 118 1953)

Starvation Phenomena were reviewed by Keys (J 138 500 1948) Under starvation conditions, the body adjusts to some extent, with concentration of serum proteins, drop in BMR, inactivity and diminished load on the heart losses of fat, muscle liver and skin and but little loss of brain and skeleton (Taylor and Keys Sci 112 215 1950) See Keys et al (The Biology of Human Starvation, Univ of Minnesota Press 1950) Edema of simple calorie starvation appears to reflect a reduction of cellular mass without change in the absolute quantity of extracellular fluid.

Experiments performed on young men subsisting on a famine diet were reported by Henschel et al. (AmJPhysiol 150: 1 0 1947) Their especial interests were the plasma

volume and extracellular fluid. These remained essentially unchanged though the weight diminished but in proportion to the diminished body weight these were comparatively increased. Clinical edema appeared not until the extracellular fluid surpassed 8 to 10% of the body weight in excess of that present in the normal person.

Dripping from the nose, without other indications of rhinitis, often heralds hunger edema (Van der Hal abs J 136: 479 1948) Hunger edema in the Netherlands during World War II was the result of caloric intake as low as 400 C. per day resulting in loss of weight of from 45 to 55% below normal (Edit: J 14 : 469 1950) Apathy and irritability were noteworthy

MALNUTRITION IN PRISONERS.—Pellagrous and ulcerative dermatitis were observed among the Polish under German occupation by Grzybowski (BJD 60: 410 1948) Nutritional disorders seen in prisoners in the Far East by Simons (BJD 61: 210 1949) included scrotal dermatitis, pellagra, burning of the throat, seborrheic dermatitis, smooth tongue, chloasma, pellagrinoid pigmentation, hyperkeratosis, pityriasis rubra pilaris, purpura and premature graying of the hair See Morgan et al. (J 130: 995 1946)

"Blood blister disease," characterized by blood filled lesions 1 cm. in diameter which burst, crusted and sometimes ulcerated, affected the skin or mucous membranes of some individuals interned at Singapore (Lander BJD 60: 1 1948)

The KZ (concentration camp) syndrome was described as a chronic stage of weakness due to famine from deficiency of calories and protein, seen in German concentration camps during World War II by Hermann and Thygeson (abs J 156: 741 1954) Asthenia, weight loss and mental symptoms were the predominating features.

Oculo-Oro-Genital Syndrome Deficiency Dermatitis of the Scrotum.—Glossitis, perlèche like inflammation and scrotal dermatitis, followed by symptoms like those of posterolateral sclerosis and by dimness of vision were observed in Singapore prisoners by Landor and Pallister (TrRoySocTropM 29 121 1935) and interpreted as being due to avitaminosis B_2 rather than pellagra, the typical dermatitis of which was wanting

The syndrome occurred in prisoners of war in the Far East (Frankland: BMJ 1: 1023 1948) Irritation was worse at night. Exacerbations were promoted by hard work, heat and intercurrent illness. Clinical varieties included a mild type, a severe dry and fissuring type, chronic maceration with fetor and an ulcerative and edematous type. Associated oral lesions *resembled ariboflavinosis. Also were seen retinal atrophy and painful, burning feet.*

Exfoliative dermatitis of the scrotum, with stomatitis and conjunctivitis, insidious in onset, affected some 75% of American prisoners of the Japanese after 6 months of an inadequate rice diet, reported Jacobs (AnnIntM 35: 1049 1951) who used the designation, "oculo-oro-genital syndrome." Scrotal dermatitis progressed through phases of pruritus, erythema, exfoliation and ulceration, affecting first the most dependent part, spreading to the perianal and anterior penile skin. It increased in intensity coming to resemble sunburn, giving rise to severe burning and itching aggravated by perspiration. Exfoliation of small, branny white scales was common, and superficial ulcers of various sizes developed in many patients. Differing from pellagra and from ariboflavinosis, the exposed skin *was not hyperpigmented, the nasolabial folds and ears were not seborrheic,* and absent were diarrhea, nausea, belly pain and neurologic symptoms. What factors must be lacking to produce these abnormalities is not as yet known, but improvement was rapid when an adequate diet became available.

Kwashiorkor is the South African name for a starvation syndrome an infantile pellagra which may be rapidly fatal associated with fatty degeneration of the liver and the development of curliness and depigmentation of the hair (Gelfand ClinProcCapeTown 5 135 1946) The diagnostic features (Hare JTropM 50 63 1947) are failure of growth, or gross loss of weight edema crazy pavement dermatosis; diarrhea, frequently steatorrhea angular stomatitis radiographic changes of deficiency disease of the gut fatty degeneration of the liver high mortality often with sudden, unexpected death. Secondary features include various types of anemia, alopecia and depigmentation of the hair, pallor and nervous irritability followed by lethargy Vitamins alone failed to help these infants reported Gillman and Gillman (AIntM 76 63 1945) but powdered hog stomach cured all the *manifestations, including the fatty livers, which they* (APath 40 239 1945) studied by needle biopsy Ventriculin 10 Gm. per day and HCl by mouth were effective (J 129 12 1945 Lancet 2 446 1946) A predominantly vegetable diet after weaning is an important cause, and skimmed milk powder at first followed by whole milk, then a full mixed diet, was rapidly beneficial stated Wills (BritJNutrit 5 265 1951) Diarrhea would stop in a few days, the liver would gradually increase in size and the serum protein values in-

creased steadily The benefits of high protein diet are indubitable (Dean BMJ 2 788 1952) but the sociologic problem where malnutrition is commonplace and ignorance and poverty are rife, is the major difficulty (Edit: BMJ 2: 821 1952) The mortality is heavy unless treatment is adequate (Brock and Autret SoAfrMJ 26 787, 1952) Hypoproteinosis must be corrected and secondary infections controlled.

The comprehensive and sympathetic essay of Williams (J 153: 1280 1953) deserves quotation.

"It must be remembered," he wrote, that the skin condition often improves when the patient does not. Also that in some patients who die, the skin condition may show marked improvement before death, even without nicotinic acid. It is important to remember that much depends on intelligent and devoted nursing Warmth, interest, and encouragement are needed, and patience and persistence in overcoming the anorexia. Small, frequent meals should be given, with a high proportion of milk protein and, at the beginning, very little fat. Food yeast or grated cheese added to the milk may make it more acceptable. It is a waste of time to investigate these diseases or to cure them in hospitals if teaching in the homes and parent education are neglected.

"Kwashiorkor is prevented by a reasonably good diet for mother and child. It is a melancholy reflection on the past defects of tropical medicine that a disease so spectacular and so widespread should have been ignored for so long

The fundamental characteristics of the syndrome are:

Retardation of growth
Dyspigmentation of hai and skin
Edema usually associated with hypoalbuminemia
Pathological changes in the li er including fatty infiltrations, necrosis and/or fibrosis
Heavy mortality if untreated or incorrectly treated
Nutritional dermatosis in a variety of patterns may be absent
Gastrointestinal disorders, variable and including anorexia, digestive upset, diarrhea and/or mild steatorrhea
Peevishness and mental apathy

"Pellagra is the main condition with which confusion is likely to arise. There is nothing to prevent the finding of mixed conditions. The differential diagnosis:

Kwashiorkor	Pellagra
Common in young children	Rare in young children
Well-developed dermatitis indicates a severe degree of the disease	Severe dermatitis may occur before constitutional signs develop
Rash has no relation to exposed areas	Skin is photosensitive. Rash is only on exposed areas and will disappear if skin is protected
In early stages skin may be bleached. N well-marked edge to rash	Early stage of rash is red, swollen, and irritating, with well-marked edge
In later stages skin is dark, soft, and crumpled and strips easily leaving raw surface	In later stages there is a dry branny desquamation
Disease may develop in patients on a diet containing some milk	Disease not described with milk in diet
Large mortality if untreated	Rarely fatal [sic; it used to be]

"Hunger edema generally decreases with rest and often increases after a balanced diet has been started, but has many features in common with kwashiorkor which differs from total undernutrition in that the actual intake of calories may be sufficient, but the excess of *carbohydrate in relation to protein is damaging. The disease differs from marasmus* i that severe illness and death may take place long before there is emaciation.

See Trowell et al. (Kwashiorkor Williams & Wilkins, 1954)

DERMATOSES DUE TO VASCULAR DISORDER

PURPURA

Purpura designates hemorrhage in the skin and mucous membranes, manifested by an eruption consisting of petechiae which are visible, hemorrhagic, reddish or purplish macules. Their blood color does not disappear under diascopic pressure In time the lesions resolve undergoing the color changes seen in bruises. Hemoglobin becomes hemosiderin, is phagocytosed and eventually carried away Purpura can occur either by diapedesis or by rhexis of the vessel wall. Blood deep in or beneath the skin is likely to appear purple rather than red

Purpura is a symptom of blood and blood vessel damaging disorders. When the cause is fairly well understood the case is called symptomatic. When the cause is obscure it is called idiopathic

Classification and Etiology—Purpuras were reviewed by Peck et al. (ADS 35 831 1937) who classified them as proposed by Rosenthal (JLab ClinM 13 303 1928) with modifications related to the response to moccasin venom *Thrombocytopenic* idiopathic or secondary to leukemia, aplastic anemia, pernicious anemia, splenomegalic cirrhosis, Banti s syndrome, Gaucher's disease and bacterial endocarditis or to drugs such as Sedormid, arsenicals, gold, chrysarobin and *Nonthrombocytopenic* in Schönlein s and Henoch's types, nitrogen retention, endocrine disorders hemophilia jaundice and systemic parasitism such as meningococcemia smallpox and syphilis; or in nutritional disturbances or in associated dermatologic conditions such as Majocchi s disease. While hyperactivity of the spleen in destroying platelets is one hypothesis regarding etiology supported by the benefits of splenectomy another hypothesis is that the cause lies in the bone marrow in view of the fact that such agents as benzene x rays, bacterial toxins and neoplastic metastases produce a reduction of platelets (Rittershofer OhioMJ 44 164, 1948)

The purpuras were classified by Kracke (SouthMJ 34 56, 1941) in a practical manner in types characterized by (1) coagulation defect, due to defect in fibrinogen, calcium or prothrombin (2) platelet defect due to inadequate formation or excessive destruction; and (3) vascular defect, due to malnutrition, intoxication or allergy Investigation of any case should include (1) complete blood count, (2) platelet count, (3) coagulation time, (4) bleeding time (5) tourniquet test, (6) clot retraction test (7) prothrombin clotting time and (8) plasma fibrinogen estimation if possible

The group ng which seemed appropriate for 153 cases studied by Rosenthal (J 11 : 101, 1933) comprised (1) Acute cases, idiopathic or associated with infection or with drug idiosyncrasy a type in which good results followed all forms of therapy splenectomy being inadvisabl until the disease is proved chronic ( ) Acute severe cases, with fever a d leukocytosis, perhaps with retinal and cerebral hemorrhages, a type ge erally *refractory* to all forms of treatment, possibly showing severe reaction to ve om (3) Cases with diminution in giant cells of the bone marrow, a type manifesti g severe reaction to venom (4) Chronic purpura, a type showing variability in severity sometimes refractory to treatment and sometimes responsive to venom, often requiring splenectomy good results being generally obtained n cases in which a persistently positive venom reaction is followed by splenectomy and some patients recover from the operation but continue to manifest purpuric symptoms.

The classific tion of Wintrobe (Clinical Hematology Lea & Febiger 1031, p. 735) divided purpuras into 2 main types, thrombocytopenic and nonthrombocytopenic Thrombocytopenic cases were subd vided into the primary type, purpura hemorrhagica, and the symptomatic types: those due to chemical, vegetable, animal and physical agents; those due to blood disorders and those due to infectio s and other disorders. The no thrombocytopenic c ses were subdivided into the allergic ones; those symptomatic of infections, chronic diseases chemical and animal agents (such as iodides mercury and snake venom); those symptomatic of avitaminosis and of v rious skin diseases such as Schamberg's and finally hereditary hemorrhagic diathesis and the miscellaneou forms. Wi trobe noted that hemorrhage is not always closely correlated with the degree of platelet reduction, and that the causes and fundamental n ture of purpuras are as yet poorly understood



Fig. 972.—Purpura.



Fig. 973.—Intracutaneous hemorrhages in rheumatic fever



Fig. 974.—Toxic purpura.

In chronic hemorrhage stimulation of the bone marrow occurs, inducing myeloid, erythroid and megakaryocytic hyperplasia and in this disease the megakaryocytes are of the young form, while platelets are reduced in the marrow as well as in the peripheral blood (Limarzi and Schleicher: J 114: 14, 1940) In differentiation from leukemia, aplastic anemia and pernicious anemia bone marrow studies are of great diagnostic value (Wiseman et al.: J 115: 8, 1940)

Poucher (J 104: 1690 1935) called attention to the fact that Bedson's antiplatelet serum will cause thrombocytopenia, but that no hemorrhage will occur until the endothelium is damaged. Yet hemorrhage occurs in the presence of a high platelet count in the Schönlein-Henoch syndrome By injecting antiplatelet serum into dogs Tocantins (ADS 34: 459 1936; AnnIntM 9 838 1936) caused the platelet count to fall to 50,000 per c.mm. in 5 minutes, and it did not return to normal for 2 to 7 days. Platelet agglutinins were demonstrated in an interesting study by Harrington et al. (AnnIntM 38 433, 1953)

Of 500 cases of purpura of various kinds reviewed by Davis (Lancet *: 160, 1943), 63% were classed by him as symptomatic Of 8 cases of purpura simplex, 72 affected women; of 79 cases of hereditary purpura 75 affected women; and of 47 cases of rheumatic purpura, 44 affected women. There were 67 senile cases, 40 cardiovascular and 41 bacterial.

Petechiae could be found if sought in half the children examined by Brown (JPediat 3. 55 1948) The highest rate of incidence was at age 10 years Lesions were more frequently seen in the springtime often associated with rheumatic pains or upper respiratory infections, perhaps being due to a streptococcus toxin.

Diagnosis of Purpura.—The noninflammatory sharply defined, painless character of the lesions, together with their color and the fact that they do not disappear under pressure should prevent confusion Scurvy must be recognized by the history the involvement of the gums, and the tendency in advanced cases for cutaneous lesions to break down and ulcerate. Gross changes in platelet count are evident in ordinary smears. In hemophilia, the bleeding time is not increased, the clot contracts, the platelets are not reduced in number and the person has been subject to attacks since infancy Capillary resistance tests were reviewed by Hare and Miller (ADS 64 449 1951)

Prognosis depends on the type and severity of the disease All except the fulminating hemorrhagic septicemic aplastic and neoplastic cases generally recover Capillary fragility tests of the tourniquet suction or snake venom type may be applied and repetitions of their use may give an idea of the progress of the disease See Physiology of blood vessels. Peck et al (J 106 1783 1936) used as a test 0 1 cc of 1 3 000 moccasin venom intradermally which may provoke local hemorrhage in an hour from the prognostic standpoint the change from a positive to a negative reaction is evidence of improvement.

SYMPTOMATIC PURPURA

Cutaneous hemorrhages may occur in typhus, meningitis, typhoid fever scarlatina, measles, smallpox, septicemia bacterial endocarditis plague, exophthalmic goiter scurvy rheumatic disease systemic lupus erythematosus, hemorrhagic disease of the newborn, spirochetal jaundice acute yellow atrophy periarteritis nodosa, chronic nephritis heart disease pernicious anemia, tuberculosis, starvation leukemia pituitary basophilism radiation injuries, thrombocytopenia, aplastic anemia amyloidosis, poisoning with various chemicals, a variety of intoxications, even severe cough, and other disorders.

Symptomatic Purpura has been described in pretibial fever an epidemic disease with a fine, red rash on the anterior skin of the legs (Bowdoin: GaMAJ 31: 437, 1942); spirochetal jaundice (Bruno et al.: J 123 519 1943; Senekjie J 126: 5 1944); intermittent hydrarthrosis (Reimann and Angelides J 146 713, 1951) secondary syphilis, a rare manifestation (Kalz: ADS 46 488, 1942) scarlatina (Fox and Earer: AmJMedSci 190: 331 1935) measles (Mills JPediat 30: 35, 1950); German measles (Magnusson: ActaMScand 126 40, 1946) malaria, 10 instances in 10,000 cases seen by Shrage and Kean (AmJMedSci 21 54 1946) pregnancy, especially in t mia thereof 64 cases having been reviewed b Chalmers (BMJ 1020 1949) who n ted the ormal bleeding time and platelet count n many cases an l the fa orable respo se to repeated sm ll transfusions pituitary basophilism (q v), a reported by Russell et al. (Lancet 2: 40, 1934); exophthalmic goiter (Bickel and Blake : SchweizMWchn 72: 411, 194.) leukemia (Whittaker: PSMMC 9: 488 1934); epidemic hemorrhagic fever (Pruitt and Cleve

AmJMedSci 225: 660 1953); and infectious mononucleosis (Wallerstein and Madison: AmPract 1: 634, 1950) When purpura accompanies infectious mononucleosis, the absence of anemia helps to xclude the diagnosis of acute leukemia (Magner and Brooks Canad MAJ 47: 35 1943 Ogilvie and Parry: BMJ : 966, 1952) Systemic lupus erythematosus has been known to simul te purpura closely (Eversole: Bull JHH 96: 210, 1955)

Purpura Due to Infection with the gonococcus wa reported by Chevallier and Bourgeois (BulMéd 43: 4 9 1928) Chronic meningococcic septicemia (q.v) caused purpura in the case of Appelbaum (AmJMedSci 193: 96 1937) Miliary tuberculosis was the cause in that of Pillsbury (ADS 35: 714 1937) Purpura associated with pulmonary tuberculosis is rare and is not due to thrombocytopenia, although the capillaries are fragile; 5 cases were reported by Dalgleish and Ansell (BJD 1: 225 1950) The purpuric spots in bacterial endocarditis often have white centers (Libman and Sachs: TransAssn AmPhys 38: 46 1923) In Gaucher's disease, hemorrhagic folliculitis and deeply seated hemorrhagic furunculosis of the legs are characteristic Chargin (ADS 35: 541 1937) said. Adrenal hemorrhage usually due to meningococcemia (q.v) has its onset suddenly with malaise lethargy feve and rapid and weak pulse; purpura is a part f the rare picture and death is likely (Waterhouse: Lancet 1: 576, 1911; Aegerter: J 106: 1715 1936)

Bites may be purpuric or may provoke purpura "purpura pulicosa," that due to fleas. Rattner (ADS 37: 605, 1913) reported a rare a d i teresting case occurring in a mulatto "0 years old: the second day after an insect bite on the forearm petechiae developed on the tongue buccal mucosa, lips, houlders and legs, the lingual lesions being vesicular

Allergic Purpura.—Allergy in relation to purpura was discussed by Thomas and Forsythe (JLabClinM 26 1105 1941) Of 10 of 64 patients with hemorrhagic purpura a family history of allergy was found in 8 thrombopenia in 2 and allergic manifestations of one sort or another in all An inhalant was shown to be the cause in 1 case, and foods in another Allergic shock is accompanied, often by a drop in the peripherally circulating platelets (Thiberge NOrlM&SJ 91 372 1939) Food allergy may cause depression of thrombocytes and purpura (Eyermann SouthMJ 28 341 1935) 3 cases cured by dietary restrictions were reported by Squire and Madison (JAllergy 8 143 1937)

Purpuric dermatitis medicamentosa (q v) includes allergic intoxication by bromides, arsenicals, Sedormid, iodides, etc. The manner of action was reviewed by Fitz Hugh (J 111: 1643 1938) who noted the possible hematologic responses of agranulocytosis hemolysis, thrombocytopenia, pancytopenia and leukemoid reaction.

Transfusions of 5000 ml. of whole blood often cause thrombocytopenic purpura reported Krevans and Jackson (J 159 171 1955)

Necrotic purpura occurs in rare instances, the resulting cicatrices having an artificial appearance it may be related to the Shwartzman phenomenon (Sheldon ADisChild 22 7 1947) Ingestion of cinchophen preceded the fatal attack of necrotic purpura in a woman who developed enormous ecchymoses and gangrenous lesions (Larrain et al. abs J 150 1041 1952)

Avitaminosis and Purpura.—Lack of vitamin C (q v) results in increased fragility of vascular endothelium. When capillary fragility is caused by the lack of vitamin C, its administration is followed promptly by a return to normal (Dalldorf and Russell: J 104 1710 1935) Vitamin P (q v) a crystalline flavone found associated with C but distinct from it was observed to control purpura when vitamin C did not (Jerslid Lancet 1: 1445 1938) Vitamin K (q v) was said to be curative of hemorrhagic cerebral symptoms and dermal hemorrhages (Poncher and Kato: J 115 14 1940)

Rutin is the crystalline flavonal glucoside of quercetin derived from buckwheat. The relationship of this nontoxic substance to vitamin P (q v) was discussed by Shanno (AmJMedSci 211 539 1946) and its value in hypertensive patients observed. Its influence on capillary fragility in a dose of 20 mg by mouth t.i.d. was reviewed by Ylaes (VaMMonth 74 56 1947) Thiocyanate intoxication proved responsive and retinal hemorrhages in hypertensive patients subsided. It seemed to have value in the prevention of progress of hemorrhagic retinopathy occurring in diabetes mellitus and arteriosclerosis (Donegan and Thomas AmJOphth 31 671 1948)

Cullen's Sign.—Blood staining at the umbilicus generally is due to ruptured ectopic pregnancy it may signify any intraperitoneal hemorrhage

Hemophilia.—Purpura, ecchymoses, epistaxis, and menorrhagia are common. There were 113 affected members in 5 generations of a family studied

by Farber (AmJMedSci 188 815 1934) none showing telangiectasia. Prolonged clotting time is a constant feature in hemophilia but this was not present in a family showing a congenital bleeding tendency affecting only the males described by Stransky and Dautalawas (ActaPediat 37 323 1949) who proposed the name parahemophilia. Bleeding was never spontaneous but resulted from trauma in these cases.

Hereditary Familial Purpura Simplex was described by Davis (Lancet 1110 1939 ; 441 1941) from his observations of 27 families in which 88 members showed spontaneous ecchymoses and 84 of these were females. The 88 purpuric persons comprised 79 with purpura simplex, 4 with Schönlein's type, 2 with Henoch s 2 with easy bruising and 1 with pseudohemophilia. Of the 88 persons, 23 gave a history of rheumatic fever 8 of rheumatoid arthritis, 15 of some other form of arthritis, and the others severe fibrositis. Platelet counts bleeding time coagulation time fibrinogen and clot retraction determinations were normal when tested. Coexistent in the woman reported by Wald a d Kissen (J 159 29 1955) was the Schonlein Henoch syndrome and response to ACTH cortisone and antihi tamines was favorable.

Hemolytic Anemia, acute and characterized by sudden onset, enlargement of liver and spleen, intense leukocytosis, abdominal pain and diarrhea or vomiting and fever was described by Lederer (AmJMedSci 170: 500 1925; 179 228 1930) It occurs in children and is best treated with small transfusions, which are generally followed by a fall in the fever A subacute form, slower in onset was discussed by Parsons and Hawksley (ADis Child 8; 184, 1933) Von Jaksch s splenic anemia is a subchronic form of hemolytic anemia. Purpura may be a symptom of a y of these. Joules and M terman (BMJ 2 160 1935) reported 4 cases of Lederer s disease cured by early transfusion.

Epidemic Hemorrhagic Fever was the name given a curious disease seen among military personnel hospitalized in Osaka in the fall of 1951 (Powell J 151; 1261, 1953 Edit J 151 1410 1953) The acute febrile disease was of abrupt onset with malaise, chills, fever, headache blurred vision, nausea and vomiting Hemorrhagic manifestations followed, with a petechial rash, marked injection of the conjunctivae hematuria and hematemesis. The white blood cell count, initially normal, rose within a few days to a leukemoid number Albuminuria was severe but jaundice did not occur The fatality rate in the first epidemic reached approximately 15% Japanese observers stated that the same disease had been seen in Manchuria during 1939-1941. The characteristic physical signs (Ganong et al. AnnIntM 38; 61, 1953) consisted of erythema of the face and neck, conjunctival injection and edema, intense pharyngeal injection, and petechiae which appeared first on the palate and later in the axillary folds. The cause was undetermined, and the treatment symptomatic. During the toxic phase the effort to palliate was challenging and sometimes unsuccessful.

Ea ly manifestations of the disease are injection of the conjunctivae and pharynx, followed by a generalized rash successively erythematous, then resembling sunburn, and later scarlati iform, confluent macular intense over the bony prominences of the face, about the neck, and, less commo ly on the shoulders, hands and scrotum (Gudgel and Grauer; AD 71 89 1955)

A sim lar condition described as Field fever and attrib ted to spirochet l in ec tion similar to if not identical with Weil s disease, was seen by Joerdens (MunchMWchr 85; 1979 1938)

Mechanical Purpura.—In some persons petechiae may appear following slight trauma or even as a result of gravity See also Senile purpura.

Menstrual Purpura.—The rash generally involves the dependent parts, may be accompanied by some fever and is symmetric recurrent and associated with scant menstrual flow and a drop in the platelet count (Smith NOrlM&SJ 90 214, 1937) The patient of Ellman and Weber (BJD 47 197, 1935) had small petechiae before the menopause and ecchymoses afterward. Patients of Minot (AmJMedSci 192 445 1936) had from 3 to 7 attacks and ceased having them spontaneously Menstrual purpura, with cyclic hemorrhages into the skin shortly after ovulation, was observed by Hamblen (Endocrinol 24 269 1939) Thrombocytopenia may or may not be present and if present, may or may not be severe When it is not present, vitamin K is likely to be helpful, Hamilton (1955) told me if it is present, transfusions and perhaps splenectomy are indicated. The administration of estrogen may or may not be helpful. The disease is rare and its cause is unknown. Some cases may be due to drug idiosyncrasy it being common enough for women to take something at that time

Nervous Purpura.—Purpuric spots may follow severe fright and also possibly various neuropathic influences. Remarkable bleeding stigmas have occurred in religious ecstasy (Klauder ADS 37 650 1938) See Dermatitis artefacta

Senile Purpura occurs in elderly individuals and commonly affects the legs forearms and backs of the hands. It was found in 60 of some 800 geri atric patients, affecting the sexes equally and unrelated to detectable dietary deficiency or to other illness, reported Tattersall and Seville (QuartJMed 74 151, 1950) The lesions, from 1 to 4 cm. in diameter were located on the ex tensor and radial aspects of the forearm and the dorsum of the hands, but not on the fingers. The purple margins were sharply defined and the skin was smooth, inelastic thin and pigmented. Minor trauma produced hemor rhages within the lesions but not in near by normal skin. There were no changes in capillary fragility tests and no response to treatment with vitamin C niacin or rutin. Histologic examination showed the epidermis to be thin the dermal papillae flattened the subpapillary elastic fibers normal, the vessels distended and tortuous but with walls that appeared to be normal Dermal collagen fibers were reduced in quantity and replaced by thick, tortuous, frag mented fibers taking the elastic tissue stain. These tangled masses comprised most or even all of the dermis in the lesions.

Solar Purpura.—Uncovered areas of blond, young dermographic skins suffered purpura after exposure to sunlight as reported by Berlin (abs ADS 40 815 1939) Pressure on the fingernail evoked subungual petechiae in his Scandinavian patients with their xerosis, freckles and telangiectases, but they appeared not avitaminotic. See Hydroa (p 716)

Toxic Chemicals causative of purpura include iodides, snake venom, mercury antipyrine chloral hydrate copaiba benzol, arsenicals, phosphorus, quinine ergot turpentine belladonna and salicylates. See Allergic purpura.

THROMBOCYTOPENIC PURPURA

Hypersplenism denotes increase in the breakdown of one or more blood elements by the spleen (Zillinger et al. J 149 24 1952) Various disease entities are recognized depending on the resultant deficiencies. The condition may be primary congenital or hereditary or secondary as a complication of chronic disease. In the primary type 4 clinical diseases result from destruc tion of platelets, red cells, neutrophils or all three and the respective names of diseases so caused are thrombocytopenic purpura, congenital hemolytic anemia, primary splenic neutropenia and primary pancytopenia. Splenectomy of which Zollinger et al. carefully described the technic usually cures any of these See Sturgis (Hypersplenism a Clinical Evaluation Thomas, 1953)

Thrombocytopenic Purpura is characterized by diminution in the num ber of platelets, a critical level of which may be set at 60 000 per c.mm., below which hemorrhage may be expected. The bleeding time is prolonged (Duke AIntM 10 445 1912 BullJHH 23 144 1912) the clot is soft and nonretractile, and capillary resistance is decreased (Nygaard et al. PSMMC 15: 753 1940) While the clotting time is normal the clot shows delayed retractility There are no morphologic changes in the blood cells, and regeneration is normal (Pemberton PSMMC 9 532, 1934) If eosinophils are numerous in the bone marrow the prognosis is better than if they are not (Schwartz and Kaplan AmJMedSci 219 528, 1950) Menorrhagia in thrombocytopenic purpura has been known to result fatally (Walsh and Donlon HMJ 93 48, 1949) In preg nancy idiopathic thrombocytopenic purpura is rare but grave when it occurs, and the infants generally show thrombocytopenia when they are newborn (Newmark J 158: 646 1955)

Acute, self limited thrombocytopenia and chronic thrombocytopenia seemed almost as distinct as different diseases to Hirsch and Dameshek (AIntM 88: 701 1951)

Purpura Hemorrhagica (morbus maculosus of Werlhof) is a severe and sometimes fatal type of thrombocytopenic purpura with extensive hemor rhages into the skin, mucosae and viscera affecting chiefly young girls. The duration of purpura hemorrhagica is from 4 to 10 weeks, although chronic cases are seen with repeated attacks over many years. The onset is usually

in childhood. Severity is variable but repeated, frequent attacks indicate the advisability of splenectomy (Vaughan and Wright J 112 2120 1939) Severe cases require splenectomy which probably removes a factor inhibiting maturation of thrombocytes (Limarzi and Schleicher J 114 14 1940) Transfusions, high protein high vitamin diet elimination of infections, viosterol iron and ultraviolet light irradiation were also recommended by Jones and Tocantins (J 100 83 1933)

PURPURA FULMINANS, which is rare is rapid and extensive in involvement. The disorder sometimes develops following scarlet fever The majority of the few reported cases have occurred in children Invariably the disease has been rapidly fatal. A boy 3 years old seen by Dwyer (J 78 1167 1922) showed symptoms commonly present in intussusception, but no tumor could be felt. The body was covered with ecchymoses of various sizes. The mucous membranes were not affected. The patient was toxic and died 9 hours after the onset of the attack. Necropsy revealed no intussusception. The viscera were pale, and hemorrhages were confined to the skin. Compare Meningococcic dermatoses (p 305)

CHRONIC PURPURA may present itself in a continuous form in which the cutaneous hemorrhages persist uninterruptedly for months or years, or in an intermittent form in which the attacks are separated by quiescent periods in which the skin and mucous membranes are apparently normal.

In infancy the disease is rare but Ström (ActaPediat 19 640 1937) was able to gather 10 acceptable examples. Congenital cases have been observed of 39 pregnancies so complicated, collated by Epstein et al. (AmJMed 9: 44, 1950) 3 mothers died and 10 infants. Surviving infants however showed return to normal of the platelet count within a few months. The ninth reported case of the essential type in the newborn in the absence of disease in the mother was seen by Boyette (SouthMJ 44: 0 1951) and recovered spontaneously A woman, whose case was reported by Urban Kl nd Hutner (J 120: 754, 1942) delivered a stillborn with purpura prior to splenectomy and had 3 normal deliveries after that operation.

Treatment—Absolute rest in bed is essential in all but the mildest cases. The patient should be handled gently and pressure and trauma should be avoided. Transfusions not only meet emergencies, but repeated small transfusions are sometimes curative Treatment varies, of course in accordance with the cause if this can be discovered The endeavor to identify causes must be systematic Lucia and Hunt (GP 11 103 1955) classified abnormalities of blood clotting as those due to abnormalities of platelets and of plasma, and abnormalities of the blood vessels as those of increased capillary permeability and of capillary fragility Platelet abnormalities might be due to their decreased production or increased removal or destruction, or due to heparin neutralization or retarded disintegration Plasma abnormalities might be hypoprothrombinemic from inability to synthesize prothrombin, deficiency of vitamin K or the presence of antiprothrombic substances or hypofibrinogenemic from inability to synthesize fibrinogen or excessive removal of it or hyperheparinemic from overdosage of anticoagulant or overproduction of heparinoid substances. Vascular abnormalities with increased capillary permeability might be due to inherited defects of vessel walls, senile weakness, vitamin C deficiency or perhaps hypothyroidism Capillary fragility might be due to allergy or to mechanical or chemical injury perhaps to hypothyroidism. Lucia and Hunt described methods for identifying and treating each of these possibilities.

Cortisone is promptly effective in arresting bleeding in cases due to allergy whether thrombocytopenic or not and without regard to the elimination of offending allergens, stated Kugelmass (NYSJM 51 2504 1951) see Adamson et al. (BMJ 2 656 1953) Cortisone or ACTH can be expected to control or diminish the hemorrhagic manifestations in about 2 out of 3 cases prior to splenectomy and even if response is only partial the risk of bleeding is diminished so that remission may be awaited or splenectomy undertaken with less urgency (Robson MJAustral 1 516 1954) When purpura is due

to allergy cortisone helps but platelet transfusion does not, according to Tullis (NEngJM 249 591 1953) and the presence or absence of antiplatelet antibodies can be determined by incubating a mixture of preserved platelets, human complement and unknown serum at 37° C counting platelets after 45 and 90 minutes.

Cortisone and ACTH were both given in 12 cases reported by Wilson and Eisemann (AmJMed 13 21 1952) with notable benefit in 5 no benefit in 7 The drugs may have especial utility in preparing a patient for splenectomy (Jacobson and Sohler: NEngJM 246 247 1952), for while no permanent remission may be obtained, yet the bleeding manifestations are generally reduced, the capillary fragility diminished and the bleeding time shortened (Stefanini et al. J 149: 647 1952) Capillary fragility diminished under treatment with ACTH when clinical improvement was obtained in cases of idiopathic thrombocytopenic purpura and systemic lupus erythematosus, reported Robson and Duthie (BMJ 2: 971 1950)

While in acute disease response to cortisone or ACTH may be especially valuable by suppressing the causative humoral or vascular factors, these drugs do not cure the condition or shorten its course. Thus in chronic disease, relapses may be expected on withdrawal of the drugs, and a relapse is sometimes not responsive to their readministration (Pariser and Wasserman ActaHaematol 12 11 1954) Their usefulness, then, is greatest in the management of exacerbations and a relapse after remission brought about by their use is an indication for immediate splenectomy

Toluidine Blue.—Excessive radiation results in the production of an anticoagulant in the blood but the hemorrhagic tendency could be prevented Allen and Jacobson (Sci 105 388 1947) found, by giving intravenously protamine sulfate or toluidine blue, substances which are apparently capable of binding heparin. Allen et al (AnnIntM 27 382, 1947) administered toluidine blue to patients with thrombocytopenia, 4 associated with subacute leukemia and 2 idiopathic. The dye dissolved in from 250 to 500 cc. of isotonic saline, in a dose of from 1 to 4 mg./kg body weight, had a dramatic effect on petechiae, but to effect lasting benefits the platelet count must be raised by transfusions or otherwise. Bleeding time is not shortened, nor is bleeding from ulcerated or denuded areas diminished. Improvement obtained with toluidine blue in thrombocytopenia is not sufficient to justify withholding splenectomy (Allen et al. J 139: 1251 1949) The value of antiheparin therapy lies in preparing for surgery palliation of acute bone marrow depression, mitigating the suffering during the last weeks of life of a patient with leukemia, or correcting the ill effect of heparin overdosage (Holoubek et al.: J 139: 214 1949) Since mast cells contain a heparinlike substance antiheparin medication may prove helpful in urticaria pigmentosa (p. 664)

Splenectomy—The substance toxic to cultures in vitro of guinea pig megakaryocytes was present in blood from the splenic vein but not in blood from the splenic artery (Torrioli and Puddu J 111: 1455 1938) Wintrobe et al. (J 109 1170 1937) called attention to the fact that splenectomy is not specific treatment, and recurrence may follow it but while being the most radical method, splenectomy is also the most effective. The operation may be performed even during an acute crisis, sometimes yielding dramatic improvement (Doan et al.: J 105 1567 1935) In skilled surgical hands, the results justify the risks (Brown and Elliott J 107 1781 1936) Splenectomy does not invariably result in cure (Pounders SouthMJ 29 317 1936)

Vaughan (BMJ 2: 842, 1937) reviewing the literature, stated that cevitamic acid may cure as many as a third of the cases, x ray over the spleen may help a half, transfusions are indispensable in tiding over the acute stage, and splenectomy which had an immediate mortality of about 7% stands a good chance of yielding permanent cure

The results of splenectomy can not be fully assessed until 3 months after operation (Robson: QuartJMed 18: 279 1949) Splenectomy was performed with success in a newborn infant suffering from the idiopathic form of the disease (Bluestone and Maslow: Pediat 4: 620, 1949) Most of the cases in children seen by Newton and Zuelzer (NEngJM 245: 879 1951) appeared to be benign and of short duration, so that the desirability and effectiveness of splenectomy were difficult to judge.

Of 75 cases studied by Evans and Perry (Lancet 2: 410, 1943), 30 were of prepubertal age of these 10 recovered spontaneously splenectomy succeeded in 5 males and failed in 4 females, and mortality was 16% Of the 45 postpubertal cases, 35 were women; only 1 recovered spontaneously splenectomy succeeded in only 7 of the 13 women who underwent it, and mortality was 40% Half of the deaths were due to subdural hemorrhage. One patient showed striking improvement during pregnancy Thyrotoxicosis was associated with purpura in 4 cases. Splenectomy was successful in a woman 8 months pregnant reported by Polowe (J 1 4: 71 1944) Splenectomy must be reserved for the idiopathic cases in adults, being a last resort in children and never used in symptomatic purpura.

Splenectomy results in the clinical cure of about 0% of cases of true idiopathic thrombocytopenic purpura severe enough to justify this procedure (QMN: J 143: 16, 1950) If the history physical examination and marrow studies have excluded the allergic drug idiosyncrasy myelophthisic and hypoplastic types of thrombocytopenic purpura which are not benefited by splenectomy and the rare hereditary form of the disease, and if the megakaryocyte count in the marrow shows a definite thrombocytic hyperplasia and the clot retraction test shows definite delay or absence of clot retraction, the clinical diagnosis of idiopathic thrombocytopenic purpura is justified. The next problem is th evaluation of the risk of splenectomy versus the risk of medical management with multiple transfusion of fresh citrated blood not over 6 hours old. The majority of cases in children respond to medical management as do some of the cases in young adults. But if the disease is chronic and recurrent or if bleeding from the gum recurs within a *few days after the clot retraction time has been brought to normal by* to 4 transfusions 6 hours apart splenectomy with removal of any accessory spleen is indicated. The operation should be performed by a surgeon skilled in this particular operation and should be scheduled a half hour aft r the la t of 4 transfusions of fresh blood given 6 hours apart The clot retraction time is much the most reliable test in following these patients, as the thrombocyte count is subject to great error

Radiotherapy over the spleen was tried by Pancoast et al. (AmJRoentg 13 538, 1925)

Long ago, Osler a d Crocker spoke highly of oil of turpentine In cases complicated with arthritis, the salicylates may be tried. Parathyroid extract given in order to obtain hypercalcemia by Lowenburg and Ginsberg (J 106: 17 0 1936), cured a case in which snake venom failed. Success with parathyroid therapy was reported in 4 cases, failure in 1 by Levine and Michelson (J 115: 160, 1940)

Snake venom in repeated mall doses wa followed by lumination in capillary fragilit a various purpuras but not in hemophilia (Peck et al.: ADS 35: 831, 1937)

Calcium chloride and calcium lactate have been recommended on theoretical grounds.

Phenylhydrazine was praised by Jacobson (SchweizMWehn 63 991, 1933); he gave the hydrochloride during meals in doses of 0.1 cc. in gelatin capsules to a total dosage of 0 7 to 1.5 cc in 28 cases without evidence of intolerance Though the number of thrombocytes was not thereby increased the hemorrhagic tendency disappeared in 19 of th 28 patie ts. In some pati nts wh at first showed no therapeutic response the medicine was repeated after several weeks.

NONTHROMBOCYTOPENIC PURPURAS

Nonthrombocytopenic purpuras include cases of purpura accompanied by articular and visceral symptoms despite the absence of pathologic changes of the blood readily demonstrable in thrombocytopenic purpura (p 755)

Henoch s Purpura (BerlKlinWchn 11 641 1874) is of this type a disease usually of early years, characterized by recurrent attacks of purpura sometimes accompanied by hematemesis melena and colic difficult to distinguish from the surgical abdomen. Urticaria and erythemas are also seen and edema of face hands and feet as in the patient of Hadley (MaineMAJ 33 184 1942) Confusion with surgical conditions was exemplified by the patient of Bisson (abs J 126 524, 1944) The exanthem was largely dependent in the 28 cases of Berggreen (abs YBD 1941 p 131) Food allergy may cause these phenomena (Hampton JAllergy 12 579 1941)

Schönlein s Purpura is accompanied by articular symptoms. Purpura rheumatica the peliosis rheumatica of Schönlein is purpura simplex associated with arthritis or erythemas of rheumatic fever (q v) Schaad (abs J 119 1147 1942) obtained rapid subsidence by giving vitamin K. Osler (see following) observed the close affinity existing between erythema multiforme (p 839) Henoch s purpura and urticaria and angioneurotic edema.

THE HENOCH-SCHÖNLEIN SYNDROME is characterized by a specific recognizable exanthem gastrointestinal and joint symptoms (Gairdner QuartJMed 17 95 1948) and occurs predominantly in children The exanthem starts

with small wheals changing into maculopapules which become dusky less raised and petechial, finally fading in a week or two They are located typically on the buttocks, lower back extensor aspects of the extremities, and the ankles and feet. Colic, bloody stools and vomiting may occur and kidney damage is often present, manifested by hematuria and albuminuria. Hematuria may rarely be the only manifestation (Lazarus JUrol 62 354 1949) Nephritis may ensue, analogous to that which sometimes follows impetigo (q v) and an occasional patient dies of renal failure.

Of Gairdner 12 cases, 10 had joint symptoms, not so severe as in rheumatic fever and not relieved by salicylates. In infancy such cases are often preceded by an upper respiratory infection associated with hem lytic streptococcus nvasion. The age range i the 44 cases reviewed by Davis (Blood 3: 129, 1948) was from 4 to 71 years. He defined the syndrome as that i which traumatic hemorrhage with o without edema may occur in the skin, subcutaneous tissues, joints or viscera in any combination. The majority of his patients suffered more than one ttack each attack lasting a few weeks, the recurrences covering periods ranging from a few months to 30 years, generally disappearing within 5 years. Occasional patient showed purpuric lesions between attacks. H held no doubt of the etiologic significance of the streptococcus.

The periodicity of the disease intrigued Reimann (J 141: 175 1949) who, like Osler (NYBJM 48: 676 1888; AmJMedSci 110 629 1895; BMJ 1: 317 1914) observed the recurrences associated with urticarial an l erythema multiforme-like phenomena. The regular ty f recurrences is striking in some patients, the cause of which remains obscure.

Anaphylactoid purpura is another but less desirable name for the syndrome for it suggests that the unknown cause lies within the defined field of allergic phenomena. Yet it is true that some cases of purpura are allergic Menthol in cigarettes apparently was causative in a case of Highstein and Zeligman (J 146 816 1951) Some cases of allergic purpura are thrombocytopenic while Schönlein Henoch cases are not. In them there may be poly morphonuclear leukocytosis but as a rule the clotting time bleeding time eosinophilia, sternal marrow and capillary resistance are not significantly changed.

Treatment is to some extent empirical, accompanied by careful search for possible causes, including allergic ones. Vitamins C and K may be tried and moccasin venom rutin and the antihistamine drugs. If the granules of the neutrophile polymorphs stain violet rather than blue, it is not likely that a pyogenic infection is present. Transfusions and irradiation of the splee[n] may be tried (QMN J 119: 918 1942 124 609 1944) Vitamin P (citri[n]) was given in doses of 50 mg intravenously daily by Jersild (Lancet 1 144 1938) to a young woman who remained symptom free while under treatme[nt] but who started to bleed when the chemical was withheld. She was not [re]sponsive to vitamin C. ACTH was conspicuously beneficial, apparently [in a] child treated by Stefanini et al (J 144 1372, 1950) although mild glom[erulo]nephritis continued. Wooley (BMJ 1 259 1952) too reported good [results] with ACTH Neither ACTH nor cortisone was of value in preventing [...] in 8 cases reported by Philpott and Briggs (ADisChild 28 57 195[3])

Cryoglobulinemia.—A woman with a history of urticaria, purpura [...] [a]nd arthralgia manifested dependent purpura, anemia and e largement [of the] spleen. Her serum protein measured 5.6 Gm. per 100 cc. when the test w[as made at] 37 C. and 4.1 Gm. per 100 t 4 C., a difference of 1.5 Gm. due t the act[ion of cold-]precipitable protein pri r to performi g the second estimation but after [...] which the patient improved, the diff rence was considerably less, report[ed ...] 67: 429 1943) Subsequently this patient wa proved to have had reticul[...]

Cryoglob linemia occurred in a patient with m ltiple m eloma and g[...] of the skin, seen by Hi efarb (AD 72: 506 1935) There are o record[s ...] shown g ryogl bulinemia, the significan e of which remains to be dis[...]

Hyperglobulinemic Purpura (Waldenstroem s Syndrome)—One [...] [a]nd 8 similar cases found in the literature by Lindeboom (Dermatolo[gica ...]) whose patient was an old man suffering from repe ted hemorrhagic e[rup]tion was preceded by a chill, and the purpuric rash f ded in a week o[r ...] several t mes ea h ear for period f 5 years. Thrombocytes wer[e ...] proteinemia with hyperglobulinemia was found. The syndrome of [re]current purpura of the legs, mild normocytic anemia and pronounce[d ...]

globulin was accompanied in the patient of Gautier and *Maurice* (*SchweizMWeh* 83 1110 1953) by calcified pulmonary and mesenteric lesions, facial paralysis and arterial occlusion of a leg the tissues of which showed sarcoid on histologic examination.

Thrombotic Thrombocytopenic Purpura.—Platelet thrombi characterized the unusual and rapidly fatal acute febrile disease suffered by a girl studied by Singer et al. (Blood 54 104) who found in the literature 11 similar cases of thrombotic thrombocytopenic purpura. See Baehr et al. (TransAssnAmPhys 51: 43, 1936); Altschule (NEngJM 22 : 477 194) Blackman et al. (J 14 546 1953); R vill and Wilson (BMJ 81 1954) Fitzgerald et al. (Blood : 519 1947) reported 3 cases of platelet thrombosis affecting the capillaries, arterioles and venules of young adult patients. Death followed the onset of symptoms within a few months.

The syndrome is characterized by fever pronounced anemia, purpura, thrombocytopenia, multifarious and fluctuating signs of central nervous system damage and progressively fatal course Platelet thrombi are histologically pathognomonic and distinguish the disease from idiopathic thrombocytopenic purpura, making diagnosis possible by marrow or skin biopsy A relation with the collagen diseases was hypothesized by Symmers (BMJ 2: 89 1952) whose 2 patients also died. Compare malignant papulosis, in which peripheral arteritis, not resulting in petechiae kills the patient.

See Dillon and Lloyd (BMJ 2: 412, 1954) case, 46 year-old woman, onset with asthenia and anorexia. March (Circ 10 43 1954) "thrombocytopenic verrucal angionecrosis, review and case report

PURPURA ANNULARIS TELANGIECTODES AND RELATED DERMATOSES

Purpura Annularis Telangiectodes—This rare type of purpura originally described by Majocchi (GiorItalmalven 31 263 1896 AfDuS 43 447 1898) is characterized clinically by the development of punctate sharply defined, rose or red, macular lesions composed of dilated capillaries, symmetrically distributed over the legs and dorsal surfaces of the feet, occasionally on the thighs, forearms and trunk (MacKee JCutD 33 129 186 281 1915) Wise (JID 5 153 1942) described the clinical features as follows

In the earliest stages, the color of the lesions is bright red, gradually assuming a darker red tint Individual lesions may be linear macular stellate or serpentine annular lesions are sometimes conspicuous but may be absent. Brownish hyperpigmentation often haloes ringed lesions or appears in scattered spots independent of megascopic vascular lesions. Later atrophy may or may not become apparent The rather abrupt formation of capillary ectases occurs without prodromal symptoms, usually appearing in showers. The dilated capillaries undergo evolutional changes, some remaining others becoming thrombosed still others perhaps rupturing There is never palpable infiltration The little red macules enlarge peripherally and merge with one another The central portions are likely to involute with atrophic cicatrization. The eruption is usually bilateral and symmetric and remissions and relapses are the rule Itching is mild or absent

Cardiovascular endocrine or other constitutional diseases of varied nature are commonly also present. *Histologic changes do not affect the epidermis, but just beneath it the vessels are dilated* some showing aneurysmal distortion and blood detritus and iron pigment are scattered in the subcutis. Small cell infiltrations, more abundant about widely dilated vessels, are evidence of perivascular inflammation. In late stages, melanin pigmentation may be found, infiltration is replaced by atrophy and obliterating end arteritic vessel changes appear

Levin and Tolmach (ADS 28 384, 1933) contributed a careful study with full bibliography concluding that the dermatosis is a manifestation of systemic cardiovascular disease.

Features common to Majocchi s disease Schamberg s disease and poikiloderma suggested to Scholtz (ADS 19 769 1929) that they may be variants of the same pathologic process. Randall et al. (ADS 64 177 1951) denied the status of entities to Schamberg s disease angioma serpiginosum, purpura annularis telangiectodes and pigmented purpuric lichenoid dermatitis because the morphologic descriptions are all about the same all are asymptomatic, benign and of unknown cause and all appear to represent cutaneous expressions of a single process or at least closely related conditions.

X ray therapy locally helps, along with, systemically a medical ' build up program giving careful attention to adequate nutrition and the elimination of focal infection Cortisone cured a man whose purpura annularis was associated with rheumatic pains, reported Kass et al (AnnIntM 41 340 1954)

See Brandweiner (MonatshpraktD 42: 640, 1906; AfDuS 88: 388, 1906; DWchn 48: 1291, 1912), Lindenheim (AfDuS 113: 649 1912) Pasini (GiornItalmalven 48 13, 1913); M Jocchi (GiornItalmalven 64 128, 1923); W y (ADS 21: 42, 1930 34 606, 1936) Degos and Meyer



Fig. 975.—Schamberg' disease. (Dr J F Perkins.)
Fig. 976.—Schamberg's disease, histologic structure. (Dr H. J Templeton.)

(DeocfrancD, 1932, p. 282) Hall and Hall (SouthMJ 32 952, 1939) Templeton (ADS 41 437 1940); Pillsbury and Nicholas (ADS 47; 589 1943); Mlakjian (ADS 50 417 1944) no essential difference from purpuric, pigmented angiodermatitis, but not synonymous with stasis; Touraine (AnnadeD 10 5, 1950) arciform telangiectatic purpura Borelli (ArchItal Dermat 25 259 1953) 3 familial cases

Schamberg s Progressive Pigmentary Dermatosis is a chronic disorder which begins with pinhead-sized, reddish points or dots forming irregular patches, which slowly extend by the formation of new lesions about the periphery The puncta in the course of time disappear leaving a brownish

brownish yellow or reddish brown pigmentation, which slowly fades. Spontaneous involution occurs in the oldest areas, and subjective symptoms are absent (Schamberg BJD 13 1 1901) Wise (JID 5 153 1942) stated that annular formations and serpentine capillary lesions do not occur that lichenoid and desquamative changes are secondary that hypercholesteremia is found in many of the patients who nevertheless appear to be in good health and that there is no relationship between Schamberg's disease and varicose veins.

Histologically the epidermis may be normal or hyperkeratotic, parakeratotic and hyperpigmented. The subepidermal papillary and subpapillary cutis contains cellular infiltrates in groups and band forms, more pronounced about the vessels of the appendages. The infiltrating cells are small round connective tissue cells, large connective tissue monocytes and polymorphonuclear leukocytes, some containing iron pigment granules. Vessels, both blood and lymph are dilated and newly formed capillaries and proliferative endarteritis are present. Intimal proliferations, especially in the subcutis, are accompanied by extravasation of blood. The elastica becomes disorganized in older lesions, especially in the area of cellular infiltration, finally resulting in reduction of the collagenous tissue and rarefaction of the elastica. With the subsidence of inflammation in older lesions there occurs a deposit of hemosiderotic granules, at first as a fine dust, later becoming clumped and taken up by connective tissue chromatophores. Absent are aneurysmal saccutation, telangiectasia and hyaline degeneration of vessel walls.

X ray therapy helps these cases. I give doses of 100 r weekly to the 4 aspects of the affected extremities, and with from 3 to 6 treatments activity ceases, although pigmentation requires considerable time to fade.

Eczematoid Purpura.—An itching purpura like disease affecting mainly adults, the majority of whom were females, manifested by recurrent eruptivity over a period of a year or more fading and leaving hemosiderinotic pigmentation, was described on the basis of 129 cases carefully followed by Doucas and Kapetanakis (Dermatologica 106 86 1953) The lower legs and thighs were affected occasionally the trunk and upper extremities. Scaling was common, papules were uncommon and *capillary fragility was increased, but* blood changes were not found. The striking peculiarity noted by Loewenthal (BJD 66 95 1954) in his study of 32 cases was the early severe, persistent itching The onset was symmetric about the ankles, with upward extension. The papules were small and lichenoid developing from bright red puncta into scaly macules and becoming lichenified. The disease represents, I suspect a variant of what I have described as simply lichenoid dermatitis (p 869) wherein the treatment includes high protein diet B_{12} injections, x ray therapy supportive elastic bandaging of the legs, and during the *acute phase* cortisone by mouth Compare atrophie blanche en plaque (p 763)

Pigmented Purpuric Lichenoid Dermatitis of Gougerot and Blum is insidious in onset, asymptomatic and characterized by tiny red or orange elevated, round papules which become purpuric and which are sepia in color due to the presence of hemosiderin. Symmetric lesions are grouped in plaques on the legs, thighs and lower trunk rarely on the arms, and never on the chest or head. Dependence of the disorder on varicosity was postulated by Ayres and Anderson (ADS 37 1062 1938) The disease responds to *elastic supportive* bandaging x ray therapy and other measures appropriate for treating lichenoid dermatitis (p 886 p 891)

See Gougerot and Blum (BSocfrançD 32 161 432, 1925, ArchdeD 1 [illegible], 1929); Castellani and Chalmers (Tropical Medicine, Wood, 1929 p. 2237) "Xanthoderma areatum," yellowish red asymptomatic lesions of legs, prevailing slowly; Wise and Wolf (ADS 31 [illegible], 1935) Michelson and Laymon (ADS 32 707 1935) Cappelli (GiornitalD 78 [illegible], 1937) Randall et al (ADS 64 177 1951) interrelationships Combes and Groopman (ADS 63 483, 1951), no benefit with vitamin C, flavones or moccasin venom; Gougerot and Blum (also BJD 65 162, 1953) review and differentiation from Schamberg disease.

Stasis Dermatitis—Some cases of varicosity of the leg veins present a *network* of tiny purplish vessels rather than the usual wide cavernous channels. The skin is likely to be stained with hemosiderin as a result of diapedesis under hydrostatic pressure which doubles the blood pressure in the ankles over that in the upper part of the body and especially following trauma or dermatitis of any cause Proliferative inflammation of the intima of the small arteries occurs in stagnation (Baker and Baker AnnIntM 9 1134, 1936) The der-

matitis appears to be due to extension of inflammation from the underlying vessels to the skin rather than to chronic passive congestion (Zimmerman ADS 34 97 1936) Miskjian (ADS 50 417 1944) stated that no essential difference exists between stasis dermatitis and capillaritis, but that the purpuric pigmented angiodermatitis of Favre referring to chronic deeply infiltrated purplish brown eruptions on the legs, is not synonymous with stasis dermatitis, which should be diagnosed only in the presence of demonstrable stasis, edema purple cyanosis and varicosity

See Touraine (BSocfrancD 44: 337 1937) capillaritis Santicandro (ArchItalD 10 133, 1934) hemosiderosis. See leg ulcer

Angioma Serpiginosum.—See Hemangioma (p. 1121)

ATROPHIE BLANCHE EN PLAQUE

A particular form of cutaneous atrophy was described by Milian (BSocfrancD 36 865 1929) and recognized as a clinical entity especially in the European literature According to Nelson (AD 71 242 1955) to whom I am indebted for most of the following These atrophic plaques almost always occur on the legs and ankles. Most frequently the patient is a woman of middle age or older who has varicosities and associated cutaneous changes, although the syndrome does occur in men and, in some instances, without accompanying vascular or cutaneous abnormalities.

The lesions are scarlike plaques that are slightly depressed and whitish to ivory-colored. Small areas of telangiectasia and hyperpigmentation often outline the plaque small angiomatous puncta may appear within and around it. Larger areas of the skin—several cm. in diameter—may become involved In approximately 70% of cases the plaques are asymptomatic and may remain so for years the patient may be entirely unaware of their existence In about 30% of the patients ulceration occurs and may recur at intervals over a long period. An angiomatous punctum frequently becomes the site of ulceration The pain and tenderness of these ulcers are severely out of proportion to their size If untreated they heal in from 3 to 4 months

Atrophie blanche en plaque is more a clinical than a pathologic entity The microscopic observation can not be considered pathognomonic. Usually the epithelium is thinned and flattened; it overlies a relatively thickened dermis that has little if any cellular infiltrate; there is a decrease in vascularity with hyalinization, thickening and intimal proliferation of the walls of the vessels that persist; few capillaries, some without patent lumens appear in groups—particularly at the peripheries of the plaques. The possibility that infection might be of causal significance is not supported by [Nelson] series. Bacterial cultures were inconclusive The failure to respond to antibiotic therapy and the lack of microscopic inflammation discount such a theory

Vesicular bullous, or hemorrhagic lesions of origin evidently similar to the atrophy may occur in the course of the disease These lesions, as well as the ulcers, eventuate in areas of atrophy typical of atrophie blanche en plaque The cause is not known, although the available data point to a vascular origin and discount an infectious basis.

Prior to hearing Nelson's presentation of the paper quoted I had not distinguished these cases from others of chronic dermatitis of the legs associated with nutritional deficiency (p. 873) Patients I have seen since have indeed shown hypoproteinemia and have continued to respond favorably to elastic supportive bandaging cortisone by mouth generous doses of vitamin B_{12} by injection, and high protein diet reinforced with iron and vitamin capsules. My patients have not been cured for they relapse when treatment is discontinued, but they have received considerable palliation.

In differential diagnosis, purpura annularis and related dermatoses and also nodular vasculitis (p 344) must be considered. These conditions all seem to have in common features of capillary and small vessel pathology and nutritional deficiencies.

See Gougerot et al. (BSocfrancD 43 1792, 1936), Milian (BSocfrancD 44 1453, 1937) capillaritis; Touraine (BSocfrancD 44 337, 1937) the capillaries in dermatology Gonin (Dermatologica 105 321, 1952) Wilson (ADS 67 237 1953); Degos (Dermatologie, Flammarion, 1953) trophic and sclerosing capillaritis.

CUTANEOUS MANIFESTATIONS OF PERIPHERAL VASCULAR DISEASE INCLUDING GANGRENE

Gangrene, which may be small or large in quantity can come about only as the result of interruption of nutrition, or toxic or traumatic destruction of the skin Causes of tissue death may be classified

- INTRAVASCULAR
  - Embolism
  - Thrombosis
- VESSEL WALL CHANGES
  - Arteritis
    - Trauma
    - Thromboangiitis
    - Periarteritis
  - Phlebitis
  - Degeneration
    - Arteriosclerosis
    - Acrosclerosis
    - Scleroderma
  - Contraction
    - Raynaud's phenomenon
    - Ergotism
    - Traumatic spasm
  - X ray radium degeneration
  - Purpuric gangrene
- EXTRAVASCULAR
  - Pressure on vessels
    - Inflammatory effusion
    - Tumors
    - Decubitus
  - Trauma
    - Burn
    - Refrigeration
  - Chemical (mineral acid, lye)
  - Factitious
  - Infectious
  - Allergic
    - Eczematous (violent)
    - Drugs (arsenical, iodide quinine)
    - Skin tests (tuberculin, Frei)
    - Anaphylactic gangrene
  - Shwartzman phenomenon
  - Trophic defects (syringomyelia, neural leprosy)

Symptomatic Gangrene may occur in intense, localized inflammatory processes. Multiple gangrenous lesions sometimes complicate severe systemic diseases, such as typhus, typhoid fever malaria and the exanthemas. See also pyoderma gangrenosum, streptococcic gangrene, staphylococcic gangrene, gangrenous balanitis dermatitis factitia. Ulceration of considerable extent may occur in syphilitic gummas, tuberculous and leprous lesions, herpes zoster, smallpox, several varieties of mycotic infection, leishmaniasis, mycosis fungoides and carcinoma. Trophic disturbances, as seen in syringomyelia, tabes and other central nervous system lesions, frequently result in gangrene. Leprosy in destroying peripheral nerves, constitutes another possible cause. See also Gangrenous dermatitis due to infection.

Toxic Gangrene.—Peripheral vasospastic gangrene due to ergotism has occurred in epidemic form. Ustilago poisoning is similar Ergotamine tartrate of some use in the alleviation of pruritus, has caused gangrene when given therapeutically; see Dermatitis medicamentosa arsenic, bismuth, ergot; Purpura necrotic.

Anaphylactic Gangrene has resulted, in isolated cases from the repetition of injections of serums, the Arthus phenomenon (p. 41)

Decubital Ulcers (Bedsores) are due to vascular compression along with the factor of debilitation of the victim The sites of predilection overlie bony prominences the sacrum, coccyx, scapulae elbows, heels and trochanters. Pressure for a prolonged time exceeding 1 5 pounds per square inch of skin will cause necrosis (Trumble MJAustral 2 724 1930)

Love (Pract 138 277 1937) described 2 types (1) the acute type rarer associated with disease of the nervous system unresponsive to treatment and rapidly fatal and (2) the chronic type the usual form postural in etiology Erythema is the early sign. In this stage dry heat, protection, and redistribution of weight bearing will prevent further progress. The further stage is congestion which does not disappear on pressure Tannic acid spray was thought useful in this stage along with protective and soothing measures. A water bed at 100 F a pillow under the knees, allowance for curvature of the spine hourly changes of posture gentle massage, elimination of wrinkles in



Fig. 977.—Symptomatic gangrene occurring in leukemia. (Dr. D. D. H. Cleveland.)



Fig. 978.—Symptomatic gangrene in arsphenamine dermatitis. (Ronchese: Am. J. Syph. 15: 366, 1931.)



Fig. 979.—Gangrene of leg, due to embolism. (From Meakins: Practice of Medicine, Mosby.)

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Fig. 979.—Gangrene of leg, due t embolism. (From Meakins Practice of Medicine, Mosby.)

bedclothes, and applications of unstretched elastoplast are worth while. In the stage of ulceration all energies must be bent toward encouraging the regrowth of tissues. Irritant medication must not be used.

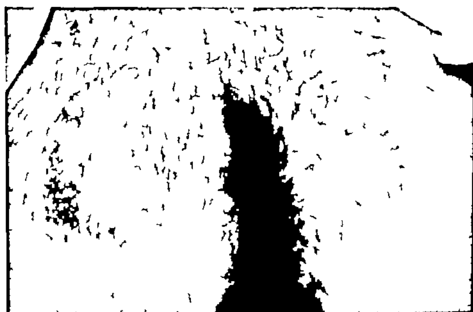


Fig. 980.—Incipient pressure sore of left buttock, developing soon after injury to the cervical cord. (Munro, New England J. M. 223: 391, 1940.)

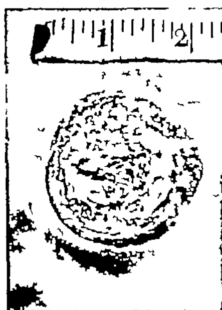




Fig. 981.—The case shown in Fig. 980 a few days later.

Fig. 982.—Pressure sore of occiput following treatment of retinal detachment.

Cope (B.M.J. 1: 737, 1939) stressed the avoidance of long-continued pressure and of minor trauma and advised keeping the skin dry and using massage and elastoplast protection in treating incipient lesions.

Stripping the area with elastoplast, as in the treatment of chronic leg ulcers, was the method used successfully in 10 cases by Carty (B.M.J. 1: 105, 1935).

Dressings wet with 1:10,000 parathiocresol in aqueous solution, supplying the sulfhydryl radicle which stimulates the healing of wounds, was recommended by Reimann (J. 94: 1369, 1930).

The care of cord injury patients was considered by Munro (NEngJM 223: 391, 1940) who moved patients by an exact, hourly time schedule. Bedsores may be excised in some instances, and a technic was described in detail by Gibbon and Freeman (AnnSurg 124: 1148 1946). In 102 patients with paraplegia, decubitus ulcers occurred, and some of them were treated by complete excision of the ulcer and regional scar tissue rotation of a flap of muscle over the débrided, exposed bone and closure with a flap of skin and fat so placed that suture lines and resultant scars were not located over the site of previous ulceration (Conway et al.: Plastic&ReconstrSurg 7: 117 1951). Excision of the underlying bony prominence was credited with the improved results of this radical method, which succeeded in o c 80% of the patients, advancing them from a bedfast to a wheel chair existence. Despite such plastic surgery there w re recurrences of ulceration in some of the patients of Langston (Plastic&ReconstrSurg 9: 543 1952) which demonstrated the need for adequate attention to low hemoglobin, low protein and low morale; injections of testosterone improved all three and helped these patients to heal.

The local pplication of dried human plasma appeared to have a good effect on the sores (Clark and Rusk: J 153: 787 1953)

An accurate method for measuring the area of ulcers and recording the progress of that course was worked out by Homburger (Sci 118: 272, 1933) using photographic projections onto cardboard, which was cut out to scale a d we ghed.

Plaster Sores, occurring beneath casts over bony prominences, usually the tibial tubercle heel or malleoli, are not fundamentally different from bed sores. Their existence may not be suspected until the odor or sight of the discharge rather than pain, gives the clue

Pressure Necrosis of the Scalp of the newborn has been observed to follow the use of obstetrical forceps (MacCarthy et al JObGyn 59 37 1952) I saw an occipital pressure sore in a woman who had undergone operation for retinal detachment, following which she lay recumbent with noteworthy obedience and resignation

PERIPHERAL VASCULAR DISEASES

Peripheral Vascular Diseases, by Allen Barker and Hines (Saunders, 1946 ed 2, 1955) is a reference of excellence quoted extensively hereinafter

Emboli and Thrombi, occluding vascular branches, cause infarction of the tissue supplied. The region, often a foot or leg becomes more or less suddenly either ischemic or cyanotic numb and tingling then painful, later anesthetic. A line of demarcation forms eventually and the dead tissue sloughs. Arterial occlusions may develop suddenly in the presence of severe infectious disease, during congestive heart failure postoperatively or in polycythemia vera or other blood dyscrasias. In patients past middle life arteriosclerosis obliterans is the first consideration in differential diagnosis. The sudden seizure with severe pain the absence of arterial pulsation, the cold white extremity with anesthesia and loss of motor power are typical early features, which will be followed by gangrene unless the obstruction proves surgically removable. Arterial thrombosis may follow acute or chronic trauma in cases lacking evidence of pre-existing arterial disease (deTakáts J 110 1075 1938) Penetrating wounds, bruises and crush injuries are causative.

Segmentary Arterial Spasm is a rare phenomenon which results from trauma. Spastic occlusion occurs within 24 hours after the injury and may eventuate in gangrene. A large artery is affected a distinction from Ray naud s phenomenon, which affects arterioles (Montgomery and Ireland: J 105 1741 1935 Cohen Lancet 1 1, 1944) Papaverine in a dose of from ⅙ to ⅓ grain given intravenously has an excellent effect in overcoming smooth muscle spasm in arterial occlusion (deTakáts: J 106 1003 1936) This drug was the most successful of those tried by Kinmonth (BMJ 1: 59 1952) who produced arterial spasm experimentally by means of electric stimulation, find ing that traumatic spasm was not relievable by sympathectomy

Endarteritis and Thromboangiitis resulting in dry gangrene may be throm boarteriosclerotic resulting in senile gangrene, obliterative or rarely syph ilitic. The lesions are usually symmetric and comparatively unresponsive to treatment; they are likely to necessitate surgery

Arteriosclerosis is a broad and loosely used category in which are placed those diseases of the arteries which lead to loss of elasticity irregular changes in appearance and structure of the medial and intimal coats and ultimately to dilatation deformity or obstruction of the lumen. These changes are primarily degenerative as distinguished from inflammatory (Allen et al. Peripheral Vascular Diseases, Saunders, 1946)

Arteriosclerosis obliterans is that type of arteriosclerosis which occurs typically in the extremities and eventuates in progressive or episodal occlusion of arterial lumina It is commonly but not exclusively a disease of the later years of life It is the most common of peripheral occlusive arterial diseases and accounts for 50 to 60% of such cases. Pathologically one finds in advanced lesions gross enlargement irregularity and tortuosity of the arteries, with considerably increased consistency and irregular thinning of the medial coat, deposits of calcium which may be in the media or at the base of atheromas, irregular atheromatous formations sometimes projecting considerably into the lumen and partial or complete occlusion of the lumen by gray or red thrombi. The 3 essential components of the lesion are atheroma, thrombosis and destructive degeneration of the medial coat. The relative proportions of these components vary considerably in various cases.

In thromboangiitis obliterans the pathologic changes include marked fibroblastic proliferation, later periarterial fibrosis, marked endothelial proliferation of the vasa vasorum in the adventitial coat, good preservation of the medial muscle without calcium deposits, and diffuse fibroblastic proliferation, especially about vasa vasorum; the intima shows no atheroma, lipid or calcium, but proliferation of the endothelium is marked a d the thrombus is extremely cellular in its organization.

Ischemia produced by arterial obstruction from arteriosclerosis obliterans may be augmented by arteriolar constriction from any cause, such as exposure to cold or the use of tobacco. It may be lessened by vasodilation produced by heat or by various vasodilating therapeutic procedures. The arterioles in extremities afflicted by arteriosclerosis obliterans are however in a condition of normal tone most of the time and are susceptible either to vasodilation or vasoconstriction. If the degree of arterial occlusion is not too exclusive, considerable improvement of the circulation may be possible as the result of arteriolar dilation. Obstruction of a large artery produces lowering of arterial pressure in the smaller vessels distal to the point of obstruction and the slowing of blood flow

Symptoms Resulting From Ischemia of tissues are mainly confined to the lower extremities. The symptoms may progress in a series of episodes with partial regression between episodes. Such symptoms include the following

INTERMITTENT CLAUDICATION a symptom and not a disease indicating inadequate supply of arterial blood to contracting muscles. It never occurs in the legs as a result of standing reclining or sitting and has no relationship to muscle cramps which patients have in bed. It is brought on only by continuous exercise and is relieved promptly by discontinuance of exercise without change of position of the affected parts. It is usually unilateral at first becoming bilateral, and continues to be worse in one leg than the other It may exist for years as the only subjective manifestation of the disease The distance that the patient is able to walk before the distress of intermittent claudication develops varies with the extent of arterial occlusion and the level at which this has taken place

REST PAIN resulting from severe ischemia and advanced disease It is usually felt first in the digits but may involve the foot and leg as well. It is noted at night commonly consisting of dull to moderate aching pain which interferes with sleep It develops after acute arterial occlusion or may result from gradually increasing arterial occlusion.

PAIN OF ULCERATION AND GANGRENE, provoking usually moderate to severe pain. Some patients do not suffer much, although opiates are required for others, some of whom ca scarcely be relieved. It persists over long periods of time and is worse at night. It is usually confined to the region of ulceration or gangrene or just proximal to it.

PAIN OF ISCHEMIC NEURITIS, occurring over large portions of the skin ad perhaps in olving the distribut on of the peripheral nerve tru ks. It occurs in the bsence of ulceration, but, if this is present, it extends proximally from the regions of ulceration for a considerable distance. It may be steady or paroxysmal and sometimes there are lightning pains. It is frequently severe and difficult to relieve It occurs more commonly among diabetic than nondiabetic patients.

OTHER SENSORY DISTURBANCES, including paresthesias, numbness and b rning Cold sensitivity is a complaint in some patients early in the disease. Muscular weakness is associated with a considerable degree of arterial insufficiency and stiffness of joints gradually develops in associaton with disuse and muscle weakness.

The Clinical Examination of a patient with peripheral vascular disease was outlined and interesting details were given by Morest (JKansMS 51 230,

1950) With respect to the history the patient may be expected to use his own terms for claudication, admitting weakness on walking or tired or achy' feelings, or cramps. The significant fact is that the patient with obliterative disease of leg vessels finds himself obliged to halt. His claudication distance may or may not vary on different days, and claudication is brought on quicker by going up-grade or by hastening His pain may be located in the lower part of the back, the hip thigh calf or arch of the foot, first appearing on one side but becoming bilateral. Pain while at rest signifies greater ischemia and is aggravated by elevation of the extremity

On inspection of the legs Morest continued, one may see that the skin is thin shiny dry and hairless. Degenerative changes of the nails may be found. Changes of skin color with changes of posture are significant in diagnosis. Good light and patience in performing the examination are important. Cyanosis present when the limbs are horizontal signifies advanced arterial insufficiency With the legs of the recumbent patient elevated to the vertical position, one requests him to flex and extend the feet at the ankles for a period of time pallor appearing within 30 seconds indicates advanced mechanical vascular defect while pallor appearing not until after some 90 seconds suggests vasoconstriction. The patient is then raised quickly to a sitting position with the legs hanging over the edge of the table and one notes the time required for the appearance of rubor and of venous filling When arteries are spastic this time interval is brief, from 2 to 4 seconds. Normally the time interval is from 5 to 14 seconds. In arterial insufficiency the time interval ranges from 15 to over 30 seconds, depending on the degree of defect present

On palpation the skin temperature may be judged with the backs of the examiner s fingers. Cold cyanosis indicates considerable impairment of arterial flow Warm cyanosis is present in venous thrombosis or cellulitis. The blanching of an area digitally compressed disappears on release of pressure rapidly when vasospasm is present, slowly when circulation is poor Disappearance of blanching means that ischemia is reversible but the failure of blanching to disappear denotes actual or imminent necrosis.

Cold mottled cyanosis in the presence of good arterial pulsation is pathognomonic of *livedo reticularis, but, in the absence of arterial pulses, it* probably means occlusion of vessels.

Examination of the circulation of the upper extremities by palpating radial and brachial arteries is straightforward Since the normal ulnar artery is not palpable, Allen s test is used to determine its patency compress with forefingers and thumbs the radial and ulnar arteries at the wrist of the patient. Cause him to clench his fist several times to render the hand relatively bloodless. Release the compression of the ulnar artery and note the palmar flush resulting from a surge of blood through the ulnar artery or abnormal delay or inadequacy of flushing The reverse Allen test is used to estimate the adequacy of the radial artery The same maneuvers are repeated but instead of releasing the ulnar artery one releases the radial artery

Palpation of the arteries of the extremities is best performed bilaterally at the same time comparing in pairs intensity volume and constancy of the arterial pulses. The deep-lying popliteal arteries are hard to feel in the obese patient. Edema obscures palpation. Anomalous location of dorsalis pedis arteries is not rare A cold examining room may explain absence due to vasoconstriction of pulses which otherwise would be normal. When small arterial pulses are found in unexpected locations, the development of collateral circulation may explain them. When pulses are not impaired or absent, obliterative peripheral arterial disease is not likely to be present.

Cool skin with adequate arterial pulsation is found in livedo reticularis, Raynaud's phenomenon and acrosclerosis. Warm acrocyanosis is present in erythromelalgia, phlebitis, lymphangiitis and cellulitis.

Ulcers appearing spontaneously not traumatic or infectious in origin, occur in venous stasis on the legs; in arterial occlusion, usually on the toes or

feet Ulcers of the finger tips are seen in Raynaud s syndrome. Ulceration of the fingernail bed is practically pathognomonic of thromboangiitis obliterans.

Marked asymmetry of involvement of the limbs favors the diagnosis of thromboangiitis rather than arteriosclerotic disease as do also the history of *superficial phlebitis, especially if it has been migratory* the occurrence in a male and the involvement of an upper extremity The diagnosis of arteriosclerosis is favored by finding the disease in other arteries, including those of the retina, by discovering calcification of the aorta on roentgenography and by the presence of diabetes, hypertension or hypercholesterolemia especially in a young individual

If hair grows normally on the dorsum of a digit in a patient with occlusive popliteal or femoral arterial disease nutritional lesions of the skin may be expected to heal but if it does not amputation is generally unavoidable (Naide NEngJM 248 179 1953)

PHYSICAL FINDINGS include impaired arterial pulsation, color changes with redness of the feet or bluish discoloration in severe cases, sometimes marked pallor of one or more toes postural changes of color with abnormal pallor on elevation and rubor on dependency with delay in return of color and in filling of veins on dependency and temperature changes due to inadequate blood supply Ulceration, gangrene and infection may develop

Spontaneous ulceration or gangrene usually develops first in the terminal portions of the digits often around the nails. Either may develop as a result of the pressure of shoes in ordinary walking Ulceration of the foot or leg is usually the result of mechanical or thermal trauma or pyogenic infection. Sometimes it develops in eczematoid lesions. When ulceration and gangrene occur in arteriosclerosis obliterans, they are usually of the dry type and accompanied by little or no systemic reaction. When diabetes is present, the lesions are more likely to be moist and there may be considerable systemic reaction with the rapid development of lymphangiitis and even septicemia. Roentgenograms of the legs may visualize calcification of the arteries or osteoporosis. Diabetes mellitus is often present, detectable by the carbohydrate tolerance test. Plasma lipids are frequently elevated and lipemia and xanthoma are common concomitants of arteriosclerotic disease.

Diagnosis.—Differentiation of thromboangiitis obliterans from arteriosclerosis in patients between 40 and 50 years of age was clarified by Silbert (J 129: 5, 1945) whose pat ents with thromboangiitis abstained from smoki g for 10 years and remained arrested during that time the patient with thromboangiitis appears younger than *his age (the arteriosclerotic, older) his hair is normally pigmented rather than gray;* the arcus senilis is absent the retinal arteries normal; the blood pressure low; the radial and temporal vessels soft; the upper extremities possibly involved; the femoral arteries perhaps occluded the vessels not calcified the blood volume diminished; the coronary artery not sclerosed the aorta normal on x ray examination albuminuria infrequent; and a history of migratory phlebitis frequent.

Spasm was differentiated from occlusion by the Landis thermal reflex vasodilation test by Saland et al. (AmHeartJ 17 581, 1939) which is accomplished by immersing the hands and forearms in water at 45 C. and recording the temperature of the great toe, a rise in wh ch should begin normally within 15 minutes reach ng 30.5 C In no case of obliterative arteriosclerosis among the 73 patients so studied did it do so. Since various degrees of spasm and occlusive disease often coexist, one cannot be sure from the observation of good response to the Landis test th t obliterative disease is actually absent. Glyceryl trinitrate, 0.4 mg given sublingually releases vasomoto tone of peripheral arteries, and a comparison of observations made before and after its administration contributes diagnostically (Foley et al. Circulation 7: 847 1953)

Phlebothrombosis may be diagnosed by a test devised by Lowenberg (J 155 1566, 1954) ot needed when the di gnosis is obvious. The sphygmomanometer cuff i placed about the calf or thigh and slowly distended. Normally discomfort is not produced before the pressure reaches 180 mm. Hg In the presence of phlebitis, pain appears at a pressure considerably below this. The pressure required to produce pain is tested on the other leg A positiv sphygmomanomet r cuff pain test is recorded when there is clear cut patient pain response to pressure ranging from 60 to 150 mm. Hg Pain is registered in the affected extremity mmediately underneath the cuff, which seems to the patient to be tighter than on the control extremity although it may in fact be 100 mm. less.

Treatment of Arteriosclerosis Obliterans involves, according to Allen et al. (Peripheral Vascular Diseases, Saunders, 1946) these general considerations (1) the disease is organic and no treatment is yet known which will open the lumen of an artery occluded by the sclerotic and thrombotic process, (2) the disease is common among old people whose capacity for healing would be poor even if ischemia were not present (3) the disease tends to be progressive once it has become manifest (4) the disease is more widespread than apparent on clinical examination and (5) it is often associated with aged persons nonvascular diseases which will terminate their lives. The basic principles of treatment include a protective regimen for the conservation of tissues of impaired blood supply and measures to promote vasodilation, to prevent vasoconstriction, to relieve pain symptomatically to encourage ulcers to heal, to limit the progress of gangrene, and to control lipemia and diabetes and so perhaps to prevent progression of the disease. Amputation is the resort when other treatment fails.

The care of the feet is fundamental and requires that the patient be given detailed instructions to avoid mechanical chemical or thermal injuries. The feet must be kept clean and should be carefully dried after bathing Toenails should be cut carefully avoiding injury to the skin. Corns and calluses should not be cut except by an expert who is aware of the hazards. Shoes must be carefully selected. Exposure to cold is to be avoided. Tinea of the feet requires nonirritating therapy The diet should be comparatively low in calories and in fat, for lipemia and obesity must be attacked and diabetes mellitus requires control if it is present. Tobacco should be interdicted. Alcohol in moderation may be permitted. Coffee and tea do not require restriction. Exertion should be limited to the capacity of the patient, avoiding intermittent claudication. Occupational hazards require consideration. The climate should be comfortable and warm.

Vasospasm and Its Relief—While mechanical blockage of vessels is of primary significance some of the symptoms and signs are due to spasm, and interruption of vasoconstrictor impulses relieves these. Ochsner and DeBakey (J 114 117 1940) reported much benefit by sympathetic block in thrombophlebitis. DeTakáts et al. (J 131 495 1946) recommended sympathectomy if temporary block gave good results, in arteriosclerosis.

When vasodilation is achieved by means of drugs, sympathetic block or sympathectomy those vessels dilate which are not occluded by organic disease. If parts of the circulatory tree suffer from occlusive disease and parts do not, but are spastic, then vasodilation may result in a shunting or by passing of partially occluded vessels. The shift in circulatory volume hemometakinesia (DeBakey et al. JMichSMS 47 636 1948) may actually diminish the circulation in tissues supplied by mechanically defective vessels, with drop of temperature and worsening of ischemia in one part of a region of which the rest is flushed. Hemometakinesia is manifested by Raynaud s phenomenon or even necrosis following the medical effort which was intended and expected to bring about vasodilation. Gangrene promptly following sympathectomy can so be explained, when it happens. Prior to sympathectomy meticulous studies must be made of the temperature response to temporary vasodilation if unfortunate results are to be avoided.

T test the capacity for vasodilation of the vessels of the foot, on need not undertake sympathetic block, an operation which the patient is likely to permit only a limited number of times. One may block the tibial nerve by injecting 5 cc. of 2% procaine at point close to and *behind the internal malleolus. This blocks both the sympathetics to* the toes nd the sensory fibers, so that, if the toes all become completely numb, the individual will simultaneously manifest all the vasodilation of which he is capable Morest (1953) told me.

Prolonged sympathetic blocking can be mai tained for several days, having inserted needles only on one initial occasion, in the treatment of thrombosis of the deep veins or f obliterative arterial disease in cases where vasospasm is considerable, Morest (1953) said, by mea of the followi g method Needles, 4 i ches long and of 18T gauge are inserted with the tips nea L1 and L— BD polyethylene plastic tubing is inserted and

then left in place, the needles being removed. The anesthetic medication, 1% procaine, cyclaine or xylocaine, is forced in 8 cc. at a dose each 4 hours day and night. The patient recognizes the feeling induced by the drug if it reaches the right place.

Lumbar sympathectomy was evaluated on the basis of extensive experience by DeBakey et al. (J 144: 1227 1950) as yielding best results in patients with least severe disease and a achieving improvement in some 75% of their cases of impending gangrene. Preliminary sympathetic block in testing the advisability of sympathectomy was not an entirely reliable procedure. They believed sympathectomy the method of choice in the treatment of peripheral vascular disease due to arteriosclerosis unless contraindicated by severe cardiac, cerebral, renal or pulmonary involvement, far-advanced and rapidly progressive gangrene, or pronounced atrophy of the extremity. Sympathectomy offers less, found Regan (NYSJM 50: 1"9 1950) when severe pain is present day and night or when gangrene is obvious. It is the method of choice in arteriosclerotic peripheral vascular disease unless there exist definite contraindications, according to Craig (PSMMC 29 143, 1954)

Chemotherapy.—Intravenous calcium proved harmless and yielded a feeling of warmth along with appreciable increase in pulse amplitude and relief of night cramps and rest pain in patients of Weichsel (AnnIntM 13: 1150 1940). Calcium must not be given a digitalized patient. Its use is now obsolete.

Histidine with ascorbic acid is more effective given parenterally than orally to relieve pain in arteriosclerosis obliterans (*Friedell et al.: J 135: 1036 1948*). *Histamine* given parenterally in a menstruum retarding its absorption was helpful in relieving intermittent claudication, for it warmed the acral skin better than paravertebral sympathetic block in the patients of Greenblatt et al. (J 141: 260, 1949). Repeated arterial infusions of histamine were recommended by Mufson (J 155 1559 1954) because they not merely released vasospasm but appeared to give impetus to structural dilation of collateral vessels. Combined with antibiotics, arterial infusions of histamine offered, he thought, the best opportunity to cure infections complicating peripheral vascular disease.

Priscoline (2 benzyl-4 5-imidazoline HCl) is a persistent vasodilator given by mouth, helpful in Raynaud's phenomenon, arteriosclerosis and frostbite (Lindquist: ActaD-V 113 93 1943; Rogers: J 140: 272, 1949 Lynn: Lancet 2: 6"6 1950)

Mecholyl, which induces vasodilation by stimulating the parasympathetics, may be given by iontophoresis with some benefit (Kovacs et al.: AmHeartJ 11: 53, 1936). Histamine iontophoresis and intravenous papaverine produce increased volume of the capillary bed and promote healing of trophic lesions, reported Mullinos et al. (AmJMedSci 197: 793, 1939)

Tetra-ethyl ammonium, a vasodilator which blocks the autonomic ganglia (Moe and Atchison. JPharmExperTher 84: 189 1945; 87 220 1946) may be given in a dose of from 100 to 500 mg intravenously (hazardous!) and 20 mg per kg. intramuscularly with considerable likelihood of improvement (Yeager et al.: SouthMJ 41: 129, 1948). The drug *causes fall of blood pressure and increased peripheral blood flow and temperature*, and it helped frostbite patients treated by Yeager et al. (SouthMJ 41: 129 1948). It seemed useful in acrosclerosis in establishing the degree of vasospasm and so clarifying the need for sympathectomy

Details of medicinal and physical therapeutic measures and the surgical aspects of obliterative vascular disease are omitted from consideration here. The article of McKittrick (J 113 1223, 1939) is commendable. Treatment of all hospitalized patients includes, he noted, bed rest careful hygiene general supportive measures, Buerger's postural exercises and intermittent venous hyperemia. By careful attention to details and by learning to live within the circulatory possibilities of their feet, many patients in the earlier stages of obliterative disease may avoid or at least postpone the onset of gangrene for many years by simple methods, but these are unsuccessful in more advanced cases.

Optimum arterial flow occurs when the extremity is kept at an angle of 15 degrees below the horizontal (Wilkins et al.: Circulation * 373 1950)

Machinery has been devised for achieving intermittent venous occlusion (Bier: *ArpathAnat 147 256; 447 1897*) by means of a cuff (*Fraser: EdinMJ 44: 733, 1937*). Passive vascular exercises utilizing intermittent suction applied to the extremity may have considerable value (Herrmann J 105 1256, 1935; Allen and Brown: ib., p. *029; Conway: J 106: 1153, 1936). The PAVEX boot received Council approval (J 106: 1986, 1936). The oscillating Sanders bed relieves pretrophic pain and the pain of ischemia, ulceration and gangrene, according to Barker and Roth (AmHeartJ 18: 312, 1939). Morest (1953) told me that the Sanders bed will reduce by two-thirds the time necessary to reduce edema due to thrombosis of deep veins as compared with resting the extremity at an elevation 30 degrees above the horizontal. One does not, of course, use the apparatus in cases of embolism.

See Starr (J 90 2092, 1928) histamine wheal delayed in appearance if blood supply is diminished. Allen (AIntM 57 601 1936) collateral circulation in arterial disease. Barker (J 104, 2147, 1935) ordinary arterial disease, hazard to toes. Scupham and deTakats (AIntM 58: 531, 1936) review of literature. Veal (J 110 786, 1938) 214 surgical cases of arteriosclerotic disease. Hines (PSMMC 13 694 1938) 280 cases of thromboarteriosclerosis obliterans, only 3 affecting radial or ulnar arteries. Horton (J 111 2184 1938) thromboangiitis obliterans, prognosis based on observations of 948 cases; Keen (AmJSurg 41 128, 1938) thrombophlebitis of male genitalia. Scupham et al. (AIntM 83 432, 1938; 64: 616, 1939)

review, bibliography surgical treatment; Ochsner and DeBakey (J 112 230, 1939) surgical evaluation; Harris (CanadMAJ 45 629 1941) sympathectomy will help if block raises skin temperature of the foot 5.4 F Fontaine and Forster (abs J 132 856, 1946), gangrene following venous disease Wright (Vascular Diseases in Clinical Practice, Year Book Publ., 1948); Anning (ADS 61 684 1950) leg ulcer in arteriosclerosis obliterans Samuels (Management of Peripheral Arterial Disease, Oxford Univ. Press, 1950) monograph Gilfillan et al. (J 154: 1149 1954) differential diagnosis of sites of arterial occlusions.

Diabetic Gangrene occurs in patients with diabetes mellitus suffering from arteriosclerosis obliterans. Slight injuries of the skin predispose to its development. The lesions are rounded, oval, or irregular in outline and may be so deep as to involve osseous as well as cutaneous tissue. The onset may be gradual or sudden. The lesions may be more or less symmetrical and the formation of the gangrenous patches may be preceded by the development of bullae. Toes are especially vulnerable, and gangrene may be initiated by minor surgical procedures such as the treatment of an ingrown nail or a corn. Gangrene is the local manifestation of a systemic disease, and mortality depends on the extent, duration systemic febrile reaction before the onset of gangrene recurrence infection and, most of all, the preoperative and post operative measures employed. Wounds in well controlled diabetics heal as satisfactorily as they do in nondiabetics (Greene et al. J 115 1518 1940)

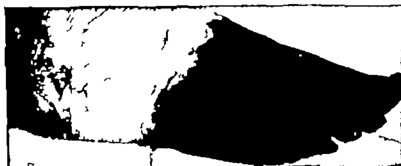


Fig. 943 —Diabetic gangrene

Of 972 cases of gangrene associated with diabetes reviewed by McKittrick (ASurg 40: 352, 1940) the sex distribution was about equal, the average age was 64, the average duration of diabetes prior to the development of gangrene was 8.7 years, the over-all mortality was 9.4% and mortality after major amputations was 14% Guides to the appropriate surgical management were set forth by Williams and O'Kane (ASurg 40: 635, 1940) in accord with their classification of the lesions as purely vascular purely infectious, or intergradiently mixed in various degrees. The majority of purely vascular superficial lesions do well without operation if infection can be avoided. Localized, noninfected vascular lesions entail no urgency but, if expected improvement does not occur calf or thigh amputation must be selected, depending on the results of examination of the circulation of the limb Marked vascular impairment together with spreading infection is the indication for urgent surgery and the thigh level is usually unavoidable. The better the circulation, the more localized may be the efforts to deal with infection.

Gangrene affecting the face in a diabetic was reported by Brier (J 103: 1704, 1934) and a similar case due to infection of the intra nasal structures was seen by Goldberg (AOtol 32: 16, 1940)

Prognosis is unfavorable but less so than before treatment with insulin was devised. *Gangrene, however generally* eventuates in amputation. Horton (J 111 2184, 1938) reported that, with recent methods of management, the expectation is that some 42% must undergo amputation and that 70% can get along for 3 years after the onset of symptoms without requiring surgical intervention, 60% for 5 years, and 40% actually for 10 years.

Proper care of the feet prevents complications in diabetes. Cleanliness, correction of defects, immediate attention to minor derangements, treatment of tinea if it is present, prevention of *constrictions and irritations* are needful. Crossing the legs is unwise. Liberal diet and control of glycemia also are valuable preventive measures. The control of infection in ischemic tissues has been simplified by the antibiotics. Tetracycline is my favorite for the purpose. Mercuric chloride poultices (1:10,000) are excellent (Peete)

See Kramer (MJ&R 132: 333 1930), signs f impending gangrene, Jordan (\aMMonth 43 455 1936) care of feet in diabetes Grodinsky (Amlburg 2 339 1938) choice of treatment, photographs Warthen nd Jordan (\aMMonth 65 63 1938), care f feet Sansted and Beams (AI tM 61, 371, 1936), ischemic neuritis in diabetic relieved by large doses of N Cl orally, Meleney (Surg 6 346, 1939), zinc peroxide treatment of gangrene Whitaker (BMJ 2: 469 1944) pressure sores developing in diabetic coma, gangrenous lesions occurring in sites of insulin i jections an en intradermally Grunberg et L (BMJ 2: 1264, 1951) recommend conservati surgery, Semple (Lancet 1 1064 1953) 100 diabetics er 50 years old, 42 with arterial disease of legs, 33 f these asymptomatic

Thromboangiitis Obliterans is a segmental, inflammatory obliterative disease of the arteries and veins which occurs almost exclusively in young men involves the extremities and, rarely the viscera also and produces ischemia of tissues and frequently gangrene (Allen et al., 1946) The pathologic picture is characteristic, involving primarily the blood vessels of the extremities and beginning in most cases in the medium-sized or small arteries, especially the posterior tibial anterior tibial, radial, and ulnar arteries (the femoral and brachial only in late and severe progressive cases) Arterioles are not affected by the typical pathologic process.



Fig 334 —Thromboangiitis bliterans, with multipl gangrenous lesions and amputation of right arm. (Drs M. C Ston and O L Castl)

The lesion is an inflammatory nonsuppurative panarteritis o panphlebitis with associated thrombosis but without necrosis of the vessel wall. The thrombus becomes organized by h avy growth of fibroblasts comparatively early and minor recanalization may occu The lesio s are segmental with normal segme ts situated between diseased segments of the essels resulting in occlusion which is permanent and usually complete so that there is de tructio o marked impairment of the function of the involved segment of the vessel. Extensive development and enlargeme t of collateral and anastomotic vessels e sue Seco dary anatomic effects of the disease are the result of m l trition of tissues, compl cated by congest on in some cases and by trauma and secondary infection. Severity is proportional to the rapidity of development and to the extent of arterial occlusio s and is inversely proportional to the rapidity and extent to which the collateral arterial anastomoses develop.

Secondary to the vascular lesions, isch mia can i duce atrophy of the skeletal muscles, osteoporosis f the foot and leg bo es, gangrene atrophy and resorption of fat atrophy of skin and distortion of nails capillary dilation and atony and ischemic neuritis.

The disease predominantly occurs in young o middle aged ad lt almost exclus vely in males, and almost exclusi ely in Hebrews. Heredity perhaps plays a part. Tobacco ha an invari bly harmful effect, but its causati e rel t o ship i u letermined. I vestigations seeking an infectious agent have proved disappointing despite the inflammatory nature of the disease.

SYMPTOMS are due to ischemia, and the outstanding symptom is pain. This is manifest as intermittent claudication, rest pain, pain of ischemic neuritis, and pain of ulceration. The inflammatory lesions of the vessels themselves are painful but not severely so. Sensitivity to cold is a frequent and often early manifestation. Paresthesias and muscle weakness occur. One finds marked impairment or absence of pulsation in the posterior tibial and dorsalis pedis arteries in most cases. Color changes include abnormal redness, particularly on dependency. Occasionally there may be cyanosis. Color changes are more significant if unilateral or affecting only certain digits. Raynaud's phenomenon may occur but its distribution is usually irregular and asymmetrical. Abnormal coldness of the skin may be conspicuous and may affect only certain digits of one extremity. The vascular lesions produce permanent arterial occlusion and normal function is not resumed either spontaneously or as the result of treatment. The lesions are segmental and may be extensive or isolated. Much of the arterial tree may be essentially normal. The disease is episodal, characterized by exacerbations and periods of quiescence. In most cases it ultimately becomes inactive, and episodes of new occlusion finally cease. Cases may be clinically divided among (1) the progressive ones, (2) the common, slowly progressive sort, (3) those with sudden occlusion of large vessels, and (4) the relatively uncommon fulminating cases of rapid progression.

DIFFERENTIATION OF ARTERIOSCLEROSIS OBLITERANS AND THROMBOANGIITIS OBLITERANS

(Allen et al. Peripheral Vascular Diseases, Saunders, 1946)

DISTINGUISHING FEATURES	THROMBOANGIITIS OBLITERANS	ARTERIOSCLEROSIS OBLITERANS
Age at onset of symptoms	Almost always under 35	Almost always over 40
Sex	Males 99 per cent	Males 93 per cent
Involvement of upper extremities	40 per cent of cases	Rare
Presence or history of superficial thrombophlebitis	40 per cent of cases	Never
Roentgenographic calcification of arteries	Absent	Present in 49 per cent of males
Hypertension	Rare in early years of disease	Present in 34 per cent of cases
Diabetes mellitus	Rare in early years of disease	Present in 20 per cent of cases
Plasma lipoids	Usually normal	Frequently elevated, especially in younger patients

Painful ischemic ulcers of the finger tips were described by Farber and McLain (ADS 64: 392, 1951) who reported studies of 2 patients with thromboangiitis obliterans limited to the upper extremities.

TREATMENT includes attempts to prevent progression of disease, efforts to produce vasodilation, mechanical devices for increasing blood flow, measures to decrease the viscosity and coagulation of the blood, symptomatic palliation of pain, procedures to increase the oxygenation of the ischemic tissues, local treatment of ulcerative and gangrenous lesions, chemicals for combating secondary infection and, finally, amputation. Protection of the parts is essential, tobacco must be interdicted, diet is of little help, and bed rest is advised during active phases of the disease, with elevation, warmth, and the avoidance of contractures. Hildenbrand (SouthMJ 38: 176, 1945) stated that fever therapy, 2- to 3-hour sessions at 103° F, relieves pain in 10 hours, and he discussed hygienic care, rest, exercise, baths, heat, sympathetic block, passive vascular exercise, intravenous saline, antispasmodic medication, intermittent venous occlusion, mecholyl iontophoresis, antibiotics, ultraviolet light and surgery.

Malignant Papulosis was the title used by Degos (AnndeD 79: 410, 1952) in describing a second case which had come under his observation of a fatal disease which may be a manifestation of thromboangiitis obliterans, an intestinal form of which was described by Köhlmeier (FrankfZtschrPath 54: 413, 1940). Degos (BJD 66: 304, 1954) undertook to distinguish his syndrome from intestinal thromboangiitis obliterans while acknowledging our ignorance of the nature and nosologic position of it.

Cutaneous lesions began with pale, rosy round, hemispheric and edematous papules, which were slightly raised and ranged in diameter from 2 to 5 mm. They became umbilicated, the central region porcelain white. The central depression enlarged and a dry white scab formed. The lesions enlarged, becoming irregular and measuring when fully developed some 3 by 10 mm. The periphery was bright red or telangiectatic, flat or slightly raised, and lesions sometimes underwent confluence and evolved toward atrophy. Attacks would occur a few new lesions appearing each week, confined to a distribution on the trunk and extremities. Eventually within a few months, an acute abdominal syndrome supervened, with intense epigastric pain and slight rigidity. Exploration at that time revealed only numerous yellowish stains on the walls of the small intestine. Death followed in a week or so. Histologically the skin lesions showed epidermal atrophy and dermal thromboses with hyaline degeneration of vessel walls and necrobiosis of neighboring tissues. The intestinal lesions also represented venous thromboses with segmentary necroses and little inflammatory infiltration saving some polymorphonuclear invasion of the thrombi and vein walls.

Skin changes accompanying intestinal thromboangiitis obliterans were noted by Laussecker (*ActaD-V 29 369 1949*). His patient, like those of Degos manifested tiny pale gray nodules with cyanotic areolae. The central skin became depressed and porcelain white, then sunken and brownish with raised, blue-red borders. Ulceration of the gut resulted in peritonitis and death.

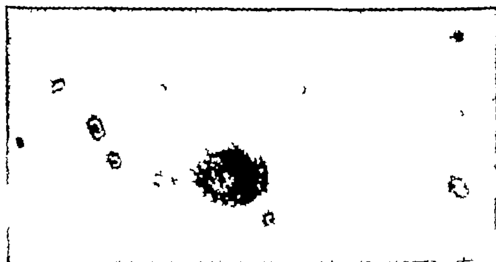


Fig [illegible].—Malignant papulosis (fatal cutaneous-intestinal syndrome) lesions as seen on chest. (Degos et al. AnndeD 79 410, 1952.)

Raynaud's Phenomenon may be defined as episodes of constriction of the small arteries or arterioles of the extremities resulting in intermittent changes in color of the extremities such as pallor cyanosis, or both. It occurs in Raynaud's disease which is rare and is a secondary manifestation more often (Hunt QuartJM 5 399 1936). It denotes functional changes in the peripheral circulation. Conditions with which it may be associated include, according to Allen et al. (1946)

Traumatic Lesions
- Occupational—pneumatic hammer disease
  - vasospasm of typist, pianist
- Following injury or surgery—
  - associated with Sudeck's atrophy
  - arteriospasm

Neurogenic Lesions
- Cervical rib and scalenus anticus syndrome
- Diseases of the nervous system

Occlusive arterial disease
- Arteriosclerosis obliterans
- Thromboangiitis obliterans
- Embolism

Intoxication with heavy metals or ergot

Miscellaneous diseases, including scleroderma and lupus erythematosus

RAYNAUD S DISEASE is a fitting diagnosis when the patient manifests (1) episodes of Raynaud s phenomenon excited by cold or emotion (2) bilaterality of Raynaud s phenomenon (3) absence, or minimal grades, of solely cutaneous gangrene (4) absence of primary disease capable of producing Raynaud's phenomenon as a symptom; (5) duration of 2 years or longer (Allen and Brown AmJMedSci 183 187 1932 Hines and Christensen J 129 1 1945)



Fig. 916.—Raynaud s syndrome with digital gangrene. (Dr Grover Wende.)





Fig 917—Raynaud's disease showing unusual deformity of toes. (Dr John W Perkins.)
Fig. 918.—Gangrene of toe in Raynaud' disease.

The typical manifestations of Raynaud s disease were described by Allen et al. (1946) as follows

> Usually the onset of such color changes is gradual, although in some instances they may be called dramatically to attention by an acute episode of pallor in one or two fingers on exposure to cold, the dead finger phe omenon. In the early stage of the disease only the tips of all fingers of both hands are involved. Later the changes in color of the ski invol e more of the proximal parts f the fingers until in the late stages the colo changes may extend back to involve the hands. Symptoms re worse in the cold season and better in the warm season. Pain is not a promine t symptom during the attack or in the interval between ta ks. Paresthesia occurs commonly d ring the tta k and consists of numbness, tingling, burning feeling of tightness, pins and needles sensation or sticking in the fingers During the attack the fingers are cold, and sensory acuity may be diminished. Slight swelling may occur and may persist even during intervals between attacks. In the progressive or advanced stages of Raynaud's disease, Raynaud s phenomenon may become disabling in its severity and frequency The attacks m y follow exposure to a

DIFFERENTIAL DIAGNOSIS OF RAYNAUD'S DISEASE, ACROCYANOSIS, LIVEDO RETICULARIS, PERNIO AND ACROSCLERODERMA (ACROSCLEROSIS)

(Allen et al. Peripheral Vascular Diseases, Saunders, 1946)

	RAYNAUD'S DISEASE	ACROCYANOSIS	LIVEDO RETICULARIS	PERNIO	ACROSCLEROSIS
Sex and age	Girls or young women in 70 per cent of cases	Girls or young women in 90 per cent of cases	Women or men of any age	Young women in 70 per cent of cases	Young women in 85 per cent of cases
Type of color change	Blue, red, white; mottled or diffuse	Blue, diffuse	Red, blue; mottled and reticulated	Blue, red; localized	Blue, red, white; mottled diffuse
Location of vascular symptoms	Fingers, toes. Nose and ears rarely	Hands usually. Feet occasionally	Legs usually, arms occasionally	Exposed surfaces, legs especially	Hands and feet
Duration of vascular symptoms	Intermittent	Permanent	Permanent	Variable, worse in winter	Intermittent
Local symptoms	None or burning pain	Usually none	None or coldness and pain	Marked itching and burning	Stiffening and tension of skin
Effect of cold	Symptoms increase	Symptoms increase	Increase of blueness	Causal, increase of redness	Symptoms increase
Effect of heat and vasodilatation	May decrease color changes greatly	Little change	Less blueness	More redness	May decrease color changes
Effect of posture and exercise	Little change	Cyanosis increases on elevation	Cyanosis decreases on elevation or exercise	No change	No change
Swelling	Slight or none	Slight or none	Slight or none	Slight, none	Slight to moderate
Necrosis and ulceration	Slight or limited or none	None	Occasionally in severe cases	Always in severe cases	Frequently in association with marked scleroderma

slightly cool environment and almost any emotional stress. Sclerodermatous changes of considerable degree may affect the involved parts and interfere with normal use of the extremity Although extensive gangrene does not occur, the gangrenous ulcerations of the tips of the digits may be persistent and may cause considerable discomfort.

RAYNAUD S SYNDROME is characterized by paroxysmal attacks of vascular spasm of unknown etiology, which cause ischemia (10% of the cases) or cy anosis (90%) of the parts involved. Pallor is due to arteriolar spasm such that blood does not enter the capillaries cyanosis when present is due to stag nation in widely dilated capillaries. It attacks females in 5 1 preference to males. Almost 80% of the cases begin before age 40 Heredity psychosomatic make-up and perhaps the endocrine balance of the patient are etiologic factors. Fingers and toes, less often nose or ears, are affected. Cooling of the body even when the hands are warm will incite an attack warming of the body will relieve an attack and an attack will be induced by exposing the hands to cold even if the body is warmed (Pearse: AmHeartJ 10 1005 1935)

Whatever the arteriolar error i that ind ces spasm, mal utrition and gangrene it is local, not of nervous origin, stated Lewis nd Kerr (Heart 15: 1929) for attacks can be produced by cooling the fi gers after preganglionic sympathectomy (Lewi : ClinSci 1: 331 1933)

DIFFERENTIAL DIAGNOSIS OF RAYNAUD S DISEASE, THROMBOANGIITIS OBLITERANS, AND ARTERIOSCLEROSIS OBLITERANS

(Allen et al. Peripheral Vascular Diseases, Saunders, 1946)

	RAYN UD' [illegible]	THROMBOAN IITIS OBLITERAN	ARTERIOSCLEROSIS OBLITERANS
Sex	Females in [illegible] per cent of cases	Males in [illegible] per cent of cases	Males in [illegible] per cent of cases
Age of onset (years)	1[illegible] to [illegible]0	2[illegible] to [illegible]0	Over [illegible]
Color changes, Raynaud' phenomenon	100 per cent of cases	[illegible]0 per cent of cases	10 per cent of cases
Postural color changes	Absent	Frequently present	Frequently present
Gangrene (if present)	Limited t small areas of skin	Minimal to extens	Minimal to extensiv
Involvement of upper extremities	Almost all cases	40 per cent of cases	Rare
Involvement of lower extremities	Usual but less frequent than of upper extremities	[illegible] per cent f cases	100 per cent of cases
Symmetry	Bilateral and symmetri	Asymmetric but usually bilateral	Asymmetric but usually bilateral
Peripheral arterial pulsations	Present	Impaired or bsent	Impaired or absent
Calcification of arteries	Absent	Usually bsent	Usually present
Superficial phl bitis	Absent	40 per cent of cases	Absent
Acrosclerosis	Sometimes present	Absent	Absent

Ga gre results when vasospasm is complicated by thrombosis (Lewis and Pickering: ClinSci 1: 327, 1934) Simpson et al. (PSMMO 5 295 1930) are among those who judge the fa lt to li primarily in the vasomotor system. Severe throbbi g pain or anesthesia may be followed by necrosis. Recurrence in an amputation stump may occur Arteriograms of the digital rteries commonly show them to be of smaller caliber than normal and often reveal filli g defects (Allen: PSMMO 12: 187 1937)

WHITE FINGERS. —This is a name for the vasospastic disorde whi h may result from the use of vibratory tools such as a pneumatic hammer (Hardgrove and Barker: PSMMO 8: 345, 1933) Dead hand o pseudo-Raynaud disease was the name used by Agate (BritJIndustM 6 144 1949) in describing cases in workers engaged in polishing metal castings with rotary tools. Cold precipitated the attacks. Coldness numbness, pallor a d cyanosis affected first the middle and ring fingers of these men, spreading in ma y of them to i vol e the fingers of both hands, the thumbs too in the worst cases.

Characteristically the condition is not symmetric, a difference from Raynaud s disease d it occurs in workmen using vibratory tools in cool surroundings, affecting the left hand of right handed person (QMN J 111: 83, 1938) The fingers manifest no pain, redness or edema, persistent sensory changes, no changes in the blood vessels except contract re and no muscula weakness, tremor or cramping If the disorder becomes well established i the winter, it cannot be expected to disappear until warm weather and so t may partially disable the man. *Discontinuing the use f the pneumatic hammer did not* relieve patients of Gurdjian and Walker (J 129: 668 1945) Of 41 patients seemingly affected with vibratory Raynaud s phenomenon, 7 were found to be suff ring from systemic

disease unconnected with the use of tools, reported Jepson (BritJIndustM 11: 180, 1954) How high frequency physical trauma produces disease is unknown. The diagnosis must be made on clinical grounds, for no satisfactory diagnostic test has been devised. The success of a medicolegal claim rests on proving that symptoms appeared for the first time after significant exposure of the right type (Edit: BMJ 1: 94 1955) for physical examination is likely to show nothing

Severe spasm of the capillaries was seen on capillaroscopy among affected workers on lasting machines by Schrank (DeutAfKlinM 187 491, 1941)

Preventive measures include the selection of workers, the changing of jobs to relieve a worker from long-continued exposure to the causative trauma, the use of insulating and shock-absorbing devices, and instruction in the proper holding of the tools (Hoerner: IndustM&S 21: 251 1952)

Treatment of Raynaud's Disease.—Vasodilator drugs are useful in allaying vascular spasm as they are in occlusive arterial disease (p 772) Psychotherapy daily rest periods nutritious diet, prohibition of tobacco protection against cold trauma and infection and the administration of thyroid if appropriate may all be helpful (QMN J 114: 1099 1940) Inunction with Nitrol (2% nitroglycerine ointment) will protect against exposure to cold for a time

The relationship of Raynaud's phenomenon, sclerodactylia and scleroderma was clarified by Brown et al. (AnnIntM 6 531, 1930) who found that acrosclerosis (q v) associated with attacks of digital ischemia is responsive to sympathectomy but advanced cases are characterized by such vascular destruction that irreparable damage having already been done sympathectomy is futile Sympathectomy is indicated when symptoms previously intermittent and mild become continuous and interfere with the activities of the patient and fail to respond to medical treatment for the operation provides permanent vasodilation and increase of blood flow and skin temperature (Adson J 106 360 1936) Surgery is advisable if little structural alteration of the vessel walls exists and if sclerodactylia is absent (deTakáts AIntM 60 990 1937) Neurosurgery failed in 22 patients of Johnson (SGO 72 889 1941)

Hereditary Cold Fingers were noted by Carwen (BMJ 1: 44, 1944) who attributed the syndrome to constitutional lethargy Psychosomatic influences are significant in some individuals whose digits are cold, pale and hyperhidrotic from an early age

Essential Arterial Spasms may occur in widely varying areas in patients who are neither hypertensive nor aged (Lian et al.: PresseM 61: 361 1953) No visible lesion can be found to explain them. They are most frequent in the extremities, where they produce numbness, cold, or even gangrene; in the retinal vessels where they lead to loss of vision lasting for some minutes, or to partial vision in which only part of a person or object is seen and in the cerebral vessels, where they result in fleeting limited paresis of an arm a leg or the tongue. The spasms sometimes follow fatigue or emotional strain, but they may occur without any apparent cause or as in most cases, they may be precipitated by exposure to cold. The attacks may occur at frequent intervals, or a single episode may be followed by years of latency; usually however there are several attacks separated by intervals of a few months. Some patients will always be affected in the same area In others, several areas may be involved, simultaneously or successively None of the patients of Lian et al. had arteritis in the affected member Arterial oscillations and sounds and arterial tension were always normal. The arteries were supple and the heart was sound. Most patients were between 35 and 50 when the first spasms occurred. Hyperexcitability either of the arterial wall or of the sympathetic nervous system, may be responsible for the occurrence of essential spasms. Treatment is necessarily symptomatic, consisting of administration of sedatives, vasodilators and antispasmodics. The prognosis must be guarded, but one may endeavor to relieve the anxiety that often accompanies the condition

PERIARTERITIS NODOSA

Periarteritis nodosa was first described by Kussmaul and Maier (AfKlinM 1 484 1866) as a rare and generally fatal disease characterized by local inflammation of arteries or arterioles with thrombosis aneurysm or hemorrhage and circumscribed necrotizing and exudative arteritis. Mesarteritis occurs, with necrosis of part of the media, polymorphonuclear infiltration and extension of the process. Males have been affected 4 times as often as females. The organs involved have been the kidney in 80% of the cases the heart in 70% the liver in 65% the mesentery in 30% the muscles in 30% the pancreas in 25% the central nervous system in 8% The lesions may be of acute, sub-

acute and chronic forms and may heal lesions in several stages may coexist. The skin is involved in about 25% of the cases, according to Lyell and Church (BJD 66 335 1954) who concluded that there are 2 forms of polyarteritis



Fig. 989.—Periarteritis nodosa, showing extensive livedo reticularis. (Ketron and Bernstein ADS 40: 929 1939.)

Fig. 990.—Periarteritis nodosa, biopsy showing degeneration of media of small artery lumen of which is partially filled with cellular débris (Drs. Ketron and Bernstein.)



Figs. 991-993.—(Ketron and Bernstein: ADS 40 929, 1939.) Fig. 991 shows atrophy of epidermis and superficial dermal tissues Fig. 992 shows thrombi in small vessels. Fig. 993 shows canalized artery representing healed stage of the disease.

nodosa the cutaneous, characterized by livedo reticularis, ulceration, muscle pains and edema and the visceral, wherein the skin, when it shows exanthemata, ecchymoses or gangrene has been involved only incidentally

Symptoms depend on the organs affected, and are characterized by acute or gradual onset, muscle and joint pains, fever abdominal pain, edema weak

ness paresthesia diarrhea insomnia chilliness, sweating purpura, angina, progressive weakness emaciation and jaundice Death results if there occurs intolerable damage to vital structures e.g., from renal insufficiency cardiac failure or rupture of an aneurysm. Subcutaneous nodules occur in some 25% of the cases (Ketron and Bernstein ADS 40 929 1939) They are of pea to hazelnut size freely movable on the subcutaneous tissues, fixed above to the skin as a rule They are evanescent Petechiae appear in 15% Alkiewicz (AfDuS 168 522 1933) assembled the findings in 36 cases with skin involvement there were present macules in 16 nodules in 15 nodes in 11 petechiae in 7 and necrosis in 5 The lesions do not commonly break down. The nodules may be pulsatile

A fairly typical eruption may occur in the chronic and more benign form of periarteritis nodosa. Livid, brown, macular and infiltrated lesions are found especially upon the lower extremities, accompanied by joint pains and papular urticaria, and in some cases by racemose lividity of a member The manifestations were exclusively cutaneous in 4 cases so diagnosed by Miescher (Dermatologica 92 225 1946) the erythematopapular and hemorrhagic exanthems resembling those seen in rheumatic fever and following focal infection. Lichenified dermatitis, erythema and subcutaneous nodules were seen by McCall and Pennock (AmJMedSci 206 652, 1943), who also noted ulceration resulting from thrombosis of cutaneous arteries. Fulminant disease featuring gangrenous lesions was diagnosed as periarteritis at autopsy in the unusual case observed by Gilman and Kaess (ADS 67 184 1953)

Probably not as rare as once thought some 400 cases of the disease had been described by 1947 (Edit: J 133 621 1947) It appears to represent an allergic reaction of the small arteries to a variety of antigens, for characteristic vascular lesions have been found in patients who died following hypersensitivity reactions to therapeutic serums and have been produced in rabbits by establishing a condition analogous to serum sickness (Rich and Gregory BullJHH 71: 1-3 194 ; 2: 65 1943) Trichinosis was apparently the cause in * cases of Reimann (J 122 74 1943) Compare nodular allergides ' (p. 1304)

Pathology—Typical circumscribed inflammation of cutaneous arterioles is found on microscopic examination of the lesions. Diagnosis may be made by biopsy of a skin nodule (Cohen et al.: J 10 1555 1936) Hemorrhage accounts for the brown stain. There are 4 stages in the pathologic processes: (1) necrosis of the innermost part of the media of small arteries or of the outer part of the media of arteries which possess vasa vasorum ( ) inflammation, with exudation of eosinophils, lymphocytes, plasma cells and polymorphonuclears, later proliferation of fixed tissue elements about the vessels and perhaps the beginnings of aneurysms or nodes, the proliferation of the intima leading to infarction; (3) the chronic stage with gran lation tissue and healing with scar (4) finally, the healed scar which is rarely seen (Arkin: AmJPath 6 401 1930; Kernohan and Woltman PSMMC 12: 654, 1937; ANeurPsych 39 655, 1938)

Suggestive, diagnostically is the finding in one urinary sediment of red cells, red cell ca t oval fat bodies fatty and waxy casts, and broad casts (Krupp AIntM 71 54, 1943) such as may occur also in systemic lupus erythematosus. These urinary changes were seen in 14 of 21 cases of these diseases by Cole (J 149: 1649 195-)

Treatment has been largely symptomatic, main reliance being placed upon rest and eradication of foci of infection. Arsphenamine has been used. Para aminosalicylic acid in large dosage seemed curative in a case of Carrick and Vonder Heide (ADS 64 359 1951) Cortisone given to 7 patients was followed by prompt relief, the fever subsiding in from 24 to 72 hours and the sedimentation rate gradually decreasing to normal but partial relapses occurred in 5 of the 7 when Schick et al. (PSMMC 25 135 1950) withdrew the hormone Cortisone induced temporary improvement with healing of arterial lesions in 2 patients who nevertheless died of cardiac and renal failure reported Baggenstoss et al. (AmJPath 27 537 1951) The remarkable influence of ACTH on healing was determined at autopsy in cases reported by Symmers and Litchfield (Lancet 2 1193 1953) One may imagine that a patient in whom the diagnosis was made early would be saved by these drugs. Lasting remissions with diminution of eosinophilia and pronounced physical improvement were obtained with ACTH by Levin et al. (JClinEndocrin 11 375 1951)

See Lamb (AIntM 14 481 1914) 2 cases, review Freund (AfDuS 151 168, 1926) review photographs Bernstein (AmJMedSci 190 317 1935) 90% fatal Spiegel (AIntM 58

993, 1936) following erysipelas; Motley (J 106: 898, 1936) urticaria, purpura, erythema nodosum; Barker and Baker (AnnIntM 9: 1134, 1936) pathology; Carol and Prakken (ActaD-V 18: 102, 1937) benign case, nodules and racemose livedo; Harkavy (AnnIntM 11: 104, 1937) arteritis; Leishman (Lancet 1: 802, 1937) 4 cases, erythema nodosum; Matras (WienKlinWchn 51: 991, 1938) nodular purpuric and gangrenous types; Harris et al. (AJDC 57: 1163, 1939) review of 101 cases; Hayne and Steiner (AmJDisChild 59: 1271, 1940) in boy of 8 following scarlatina; Keith and Baggenstoss (JPediat 18: 494, 1941) 7 children; Jones (AnnIntM 16: 920, 1942), symptoms, 14 cases, average length of life after onset 11 months; MacKeith (BMJ 1: 139, 1944) localized subcutaneous edema of limbs with muscular weakness; Michelson and Winer (ADS 52: 292, 1945) histology of tibial periosteal lesion; Wilson and Alexander (JLabClinM 30: 195, 1945) 300 cases, association with topic disorders; Melczer and Venkei (Dermatologica 97: 314, 1947) 5 cases with skin manifestations; van Rijssel and Meyler (ActaMScand 132: 251, 1948) arteritis from sulfonamides; Zeek et al. (AmJPath 24: 889, 1948) periarteritis nodosa and hypersensitivity; Rose et al. (AnnIntM 32: 1114, 1950), 8 cases, 5 necropsies; Adelson (JPediat 38: 346, 1951) in infants; Walton and Ashby (BMJ 2: 1310, 1951) fulminant case with gangrene, recovered; Slinger and Starek (ADS 63: 461, 1951) case improved on Aureomycin; Barnum et al. (Angiol 2: 280, 1951) following thiouracil; Goar and Smith (AmJOphth 35: 1619, 1952) ocular manifestations; Jackson and Kass (AnnIntM 36: 282, 1952) hypothetical relation to sarcoid; Simpson et al. (BMJ 2: 639, 1952) recurrent purpura and nodule, case remained in remission after ACTH; Bureau and Barriere (AnnDeD 81: 601, 1954) man with bullous, erythemato-squamous, and small red papular lesions; Malkinson and Wells (AD 71: 402, 1953) cortisone given 5 months followed by apparent cure.

Wegener's Granulomatosis, to which my attention was called by George Andrews (pers. comm., 1955) is a rare syndrome characterized by fever, necrotizing granulomatous lesions of the respiratory tract, generalized arteritis and focal glomerulitis. Clinically it is recognized by the combination of severe sinusitis or pulmonary inflammation, variable symptoms of arteritis and terminal renal insufficiency. Accrediting the first case to Klinger (ZtschrPath 42: 455, 1931) and the formulation of the disease as an entity separable from the usual form of periarteritis nodosa to Wegener (BeitrPathA at 102: 36, 1939), Fahey et al. (AmJMed 17: 168, 1954) wrote: The disease affects men and women of all ages, most frequently in the fourth and fifth decades. It seems to appear in persons of good previous health, generally without histories of allergy, asthma or exposure to sulfa drugs. The duration is brief, 6 months on the average, and the outcome in recognized cases would appear to be fatal. The first symptoms are often referred to some part of the respiratory tract. There may be a persistent sinusitis or rhinitis which in many instances is severe enough to cause ulceration and bony or cartilaginous destruction. Or attention may first be directed to the lungs because of chronic cough, hemoptysis or unresolving pneumonia. In many cases constitutional symptoms are out of proportion to the intensity of the local process, and the patient may first seek help because of weakness, fever or progressive weight loss. Whatever the local lesion, it generally does not respond to the usual therapeutic measures and sinusitis persists despite drainage and chemotherapy, pulmonary lesion progress to the point where surgical intervention is necessary. With extensive cartilaginous and bony destruction in the upper respiratory tract, saddle nose deformity may appear; orbital involvement may result in papillitis, chemosis and exophthalmos, or extension downward may establish fistulous communications with the buccal cavity. The inflammatory lesion is not limited to these areas, and patients may suffer symptoms referable to other organs. Episodes often transient, of arthritis, neuritis, carditis, parotitis and prostatitis have been seen.

Skin and oral mucosal lesions are common in the form of petechia, granulomatous masses or ulcers. The syndrome may simulate sarcoidosis, tuberculosis, syphilis, tularemia, glanders, lymphopathia venerea, or histoplasmosis and other deep mycoses. The cause and treatment are unknown.

ARTERITIS OF THE TEMPORAL VESSELS

A group of cases of arteritis limited to the temporal vessels was observed by Horton et al. (J 106: 240, 1936) who described them as being characterized by their nonfatal nature, by their attack upon elderly persons, by the severely painful, circumscribed, reddish, tender nodules in tortuous and enlarged temporal arteries, and by the accompanying headache, malaise, lassitude, weakness, fever, night sweats, anorexia, loss of weight, anemia and difficulty in chewing. Spontaneous recovery may be hoped for after illness prolonged for from 4 to 6 months (Hoyne: IllMJ 9?: 293, 1947). Extreme persistency with severe headaches and consequential, protracted misery of the patients were noted by Jennings (BMJ 1: 443, 1948). The disease had not been found in patient younger than 55 years of age when Dantes (J 131: 1265, 1946) noted that women are affected twice as frequently as men.

The disease is remarkably localized, though retinal and oral involvement have been identified. To embolism with mental and central neurologic disturbances, and perhaps visual difficulties, were features emphasized by Robertson (BMJ 2: 168, 1947). Necrosis of the sclera occurred in a man of 31 years who had previously suffered from an allergic reaction to sulfonamid medication (Harbert and McPherson: AmJOphth 30: 7?7, 1947). Glaucoma developed in the patient of Andersen (ActaMScand 128: 151, 1947); optic atrophy in the patient of Anderson et al. (SouthMJ 41: 420, 1948). The patient of Meade et al. (SouthMJ 43: 40, 1950) became blind. The disease has been known to produce ischemic necrosis of the scalp (Kendall: BJD 2: 418, 1953). Arteriosclerosis of the radial and brachial arteries and death from cardiovascular accidents were seen by Cole (BritHeartJ 10: 26, 1948).

Histologically multinucleated giant cell inflammation in focal distribution is the interesting feature (Dick and Freeman: J 114: 645, 1940; Edit J 131: 669 1946) Biopsy was followed by increase of pain in the patients of Vandivier and Ritchey (JIndianaMA 38 289 1945); their patients, asthenic, hypertensive blue-eyed and white haired, were not users of tobacco.

There is some therapeutic response to large doses of potassium iodide. Excision of the artery is the most effectual procedure. Temporary relief was obtained in 4 cases by periarterial injections of procaine by Roberts and Askey (J 137 697, 1948) A relation to periarteritis nodosa was postulated by Trias (abs J 143 1032 1950) who commented on the sequence of replacement of the arteritis syndrome by asthenia suggestive of adrenal insufficiency, and there was dramatic response to ACTH in the case of Tate and Wheeler (JkansMS 52 374 1951) the value of which was confirmed by Kristensen (abs J 149 1166 1952) and Aveling and Stevenson (Lancet 2: 610 1952)

See Horton and Magath (PSMMC 12 343 1937) description, Justin-Besançon (abs J 135 181, 1948) French woman helped by sulfonamides, Crosby and Wadsworth (AIntM 81 431, 1948), 48 reported cases to date, case associated with dissecting aneurysm; Wolf (Münch-MWchr 93 167 1951), histopathology Turner and Van Horn (J 149 826, 1952) relief of head pain by surgical division of temporal arteries; Ruiter (ActaD-V 32; 374 1952) allergic vascular inflammation Oosthuizen and van Wyk (SoAfrMJ 28 310, 1954) ACTH notably beneficial symptomatically, not histologically. Heptinstall et al. (JPathBact 67: 507 1954) giant cell temporal arteritis, 14 cases, 8 with visual disturbances and 6 with pain in limbs and joints.

DERMATOSES DUE TO PIGMENTARY DISORDER

ABNORMALITIES OF SKIN COLOR

Color changes are seen in almost every dermatosis. They may be classified as to whether the origin is outside the body or within it and as to whether the pigment substance is body-own or chemically foreign. The arrangement may be subdivided further as to whether the change represents disordered growth or disordered chemistry whether it is localized or generalized, and whether it results in an intensification or a diminution in pigmentation.

For example stains and tattoos are localized, color-increasing biochemically foreign, externally originating respectively supradermal and intradermal abnormalities of pigmentation. Argyria exemplifies generalized color increasing, biochemically foreign, internally originating abnormality of pigmentation. Suntan exemplifies localized, color increasing externally originating abnormality of body-own, iron free pigment. Schamberg's disease exemplifies localized, color increasing internally originating abnormality of body-own, iron-containing pigment. Jaundice exemplifies generalized, color-increasing internally originating abnormality of biochemically body-own substances. The monobenzyl ether of hydroquinone induces localized, color-diminishing externally originating abnormality of body-own melanin pigment. Albinism exemplifies generalized, color-diminishing, internally originating abnormality of body-own pigment. Melanotic nevi exemplify localized, color increasing internally originating abnormality of body-own pigment, due to disordered growth. The pursuit of this argument is left to the ingenuity and discretion of the reader

Classification.—A number of agents and diseases provocative of pigmentary changes are listed as follows

Physical, Chemical, Parasitic

- Sunlight
- X rays, radium
- Radiant heat
- Friction
- Photosensitization
- Stain
- Tattoo
- Drug eruptions: As, Bi, Hg, Pb, Ag, Au, quinacrine, ACTH dinitrophenol, phenolphthalein, picric acid, TNT
- Pediculosis, animal parasites
- Pinta
- Syphilis
- Tinea versicolor erythrasma

Nutritional and Metabolic

- Avitaminosis
- Chronic illness, malnutrition
- Xanthoma
- Carotinemia
- Urticaria pigmentosa
- Jaundice
- Pernicious anemia
- Hemochromatosis
- Ochronosis

Endocrine

- Pregnancy
- Menopause
- Thyroid dysfunction
- Pituitary basophilism
- Adrenal cortex tumor
- Addison's disease
- Acanthosis nigricans

Inflammatory

- Dermatitis venenata
- Chronic dermatitis
- Lichen chronicus simplex
- Exfoliative dermatitis
- Erythema multiforme
- Lichen planus
- Dermatitis herpetiformis
- Poikiloderma
- Pruritus

Hemorrhagic

- Purpura
- Majocchi disease
- Schamberg's disease
- Pigmented purpuric, lichenoid dermatitis
- Stasis and varicose dermatitis

Developmental and Neoplastic

- Darier's disease
- Congenital dyskeratoses
- Mongolism
- Osteodystrophia fibrosa
- v Recklinghausen's disease
- Mongolian spot
- Blue nevus
- Incontinentia pigmenti
- Freckle lentigo
- Pigmentary nevus, melanoma
- Seborrheic keratosis
- Basal cell carcinoma, pigmented
- Xeroderma pigmentosum
- Kaposi's sarcoma
- Lymphoblastoma
- Polycythemia

Autochthonous Pigmentations *of the skin are of two general classes* hemosideroses (iron-containing see also hemochromatosis and Schamberg's disease) and melanoses (iron free see also lipomelanic reticulosis and ochronosis) This chapter is concerned largely with the abnormalities of melanotic pigmentation while nonmelanotic disorders are discussed individually elsewhere Freckles and lentigines belong in the melanotic group deposits of pigment are found in the lowermost epithelial cells. The basal layer contains two types of cells, the epithelial, which may hold pigment granules and the melanoblastic dendritic elements which elaborate it. The immature melanin forming cells are melanoblasts and the mature *melanin forming cells* are melanocytes cells with phagocytized melanin are macrophages (Fitzpatrick and Lerner Sci 117 640 1953) See Anatomy pigment (p 8)

Melanin Chemistry and Related Biologic Studies comprise an extensive chemical specialty initiated in modern fashion by the studies of Bloch (Ztschrf PhysChem 98 226 1916) who discovered the ability of dihydroxyphenylalanine dopa to oxidize into melanin certain particles within pigment cells. Further studies by Bloch (AfDuS 124 129 209 1917 135 77 1921 HandbHuG 1 434 1927) elaborated on the formation of pigment in the skin and the pathogenesis of vitiligo Brief mention is given here of certain relatively recent contributions.

An interesting review of pigmentation was published by Jacobsen (APath 17: 141; 301 1934) Studying the response of the skin to exposure to thorium X, dopa oxydase was found to precede by several days the appearance of pigment itself (Peck: ADS 21 916 1930) The technic of the dopa reaction as used to determine the presence of cells containing dopa oxydase was given by Laidlaw and Blackberg (AmJPath 8: *491 1932)* A technic for demonstrating the dopa reaction in paraffin sections was presented by Becker et al. (ADS 31 190 1935) who located in the epidermis 3 types of cells: the basal epithelial the pigmented and the nonpigmented. Oxidation accounts for the darkening of skin pigment, according to Miescher and Minder (Strahlenther 66: 6 1939) Nonspecificity of the dopa reaction was alleged by Sharlit et al. (ADS 45: 103, 1942) Tyrosine could be oxidized to form melanin in vitro by the influence of *ultraviolet light* in the presence of iron salts, discovered Rothman (JID 5: 61, 1942) The significance of copper as a possible catalyst was investigated by Flesch (JID 11: 157 1948)

Ultraviolet irradiation of tyrosine in solution may result in the formation of dopa, which then catalyzes the oxidation of tyrosine to melanin in the presence of tyrosinase (Fitzpatrick et al.: ADS 59 620 1949) Nonmalignant pigment cells in normal skin require activation of the tyrosinase system by a stimulating factor such as ultraviolet light, in order to form melanin when incubated with tyrosine; but the cells of malignant melanoma appear to possess the ability to form melanin when incubated with tyrosine without the need for a stimulating factor observed Fitzpatrick (ADS 63: 379, 1952) The review article on chemistry of pigmentation by Burn (BJD 63: 431 1951) deserves mention. He related pigmentation to the function of the pituitary body normally held in check by the adrenal cortex. A melanin-stimulating hormone has been obtained *from the* pituitary gland, and the increased pigmentation of Addison's disease and pregnancy may be due to its increased production (Lerner et al.: JID 1: 337 1953) The hormone induced hyperpigmentation in normal individuals, but not in spots of vitiligo. See exhibit of Lerner et al. (ADS 70 669 1954) also Lerner et al. (JClinEndocrinol 14 1463 1954) noting vitiliginous areas did not darken, although intervening normal skin did, after MSH was given.

See Gordon et al. (Pigment Cell Growth, Academic Press, Inc., 1953)

Pigmented and nonpigmented areas of the skin of guinea pigs were interchanged by grafting by Fessler (BJD 53 201, 1941) When white skin was moved to a pigmented area, the grafts generally failed to take. When pigmented skin was grafted onto a nonpigmented area, it usually took, and pigment cells invaded the adjacent nonpigmented epidermis, indicating that melanoblasts have a greater power to migrate than do epithelial cells. Grafts of embryonic tissues studied by Willier (AnnSurg 116: 598, 1942) also showed that melanoblasts have the power of migration. They migrated, a fact from their place of origin in the neural crest of the embryo and if before reaching their destination they were removed, then in the adult animal the hair or feathers were white. Willier believed that the direction, differentiation and action of the melanoblasts were influenced by hormones. The origin of pigment cells in the neural crest *is pertinent* in interpreting the histogenesis of pigmentary nevi (p. 1068)

Dopa oxydase is actually tyrosinase the presence of which in human skin was demonstrated by Fitzpatrick et al. (Sci 112 223 1950) It is the enzyme involved in the oxidation of both tyrosine and dopa to melanin, according to Fitzpatrick and Lerner (ADS 69: 133, 1954) whose essay discussed the biochemical basis of normal pigmentation and of certain pigmentary disturbances which they undertook to explain as *alterations of*

biochemical factors affecting melanin formation within the melanocyte. Melanin pigments result from polymerization of the oxidation products of orthodihydroxyphenyl compounds to insoluble substances of high molecular weight. The only compound in human beings giving rise to melanin appears to be dopa. Melanin may be defined as the pigment which results from the enzymatic oxidation of tyrosine by tyrosinase, which is attached to the cytoplasmic mitochondria of the dendritic pigment cells the only cells in which tyrosinase activity can be demonstrated histochemically These cells form a syncytium along the epidermal-dermal junction. Embryologic studies [aforementioned] indicate that they originate in the neural crest and migrate to the epidermis. When these melanocytes are destroyed, permanent depigmentation results. Tyrosinase in human epidermis requires copper for its activity and agents which combine with copper inhibit melanin formation. Thiouracil and BAL inhibit it as do the monobenzyl ether of hydroquinone and other parahydroxyphenyl compounds when applied locally Pigmentation is influenced by the pituitary for ACTH contains a melanocyte-stimulating hormone (MSH) as a contaminant. In phenyluria, there is a relative deficiency of tyrosine so that decrease of pigmentation results from a mechanism that blocks the intermediary metabolism of phenylalanine and tyrosine.

In albinism there is a deficiency of tyrosinase in melanocytes, but it is not true that in albinism melanocytes are absent Tissue explants were incubated with radioactive tyrosine by Kukita and Fitzpatrick (Sci 121: 893, 1955): labeled tyrosine was converted into labeled melanin by the tyrosinase of the melanocytes of hair matrix, and its presence was demonstrated by autoradiography after the surplus labeled tyrosine was rinsed out. Such experiments with hair bulbs from an albino showed that no melanin was formed from the labeled tyrosine, confirming the absence of tyrosinase from the demonstrable melanocytes of the albino.

Histologic Aspects of Melanogenesis were studied by Becker et al. (ADS 65: 511, 1952) They confirmed the finding at the epidermal-dermal junction of no pigmented melanodendrocytes as described by Medawar (Nature 148 783, 1941) and Billingham (JAnat 82: 93, 1948; 83: 109 1949) These cells divide by mitosis and are found in normal, vitilliginous and albino skin. Variations in pigment formation are due to variations of the function of these cells, not of the number of them. They are identical with the Langerhans cells and form a syncytium at the level of the basal layer their dendritic processes extending to the granular layer They are the only epidermal cells in which tyrosinase activity can be demonstrated histochemically and are the only epidermal cells which produce melanin This is apparently released from the dendrites into the epidermal cells of layers superficial to the basal layer Melanin granules in the deeper epidermal layers are always within these cells and their dendrites, although the latter when unstained, may appear to constitute a part of the prickle cells, which they are not.

See Becker (ADS 16 259, 1927) dendritic cells; Montgomery (JLancet 56 472, 1936) generalities; Goldsmith (ClinJour 67 397 1938) review Becker (Clinics 3 846, 1944) varieties Albrecht (CurMDig Aug., 1946, p. 17) review; Becker (JID 7 361, 1946) comparative anatomy of melanin pigmentation; Becker (Dermatologic Investigations of Melanin, N Y Acad. Sci, 4 82, 1948) Lutz (Dermatologica 96 232, 1948) review anomalies of pigment, hair nails, secretions, Rodel (ADS 68 646, 1953) improved dopa technic; Dowling and Whitlock (Pract 168 461, 1952) melanogenesis and disorders thereof, review

NEOPLASTIC MELANOTIC HYPERPIGMENTATION

Pigmented Nevi (q v) may be elevated with their content of melanocytic nevus cells, or they may be macular when they consist of a relatively small accumulation of melanocytes. Macular pigmented nevi are lentigines and are to be distinguished from freckles

GENERALIZED PIGMENTATION followed the surgical removal of a pigmented hairy mole in the patient of Trueblood (NoWM 46 199 1947) who found 2 similar cases in his search of the literature Another was presented by Leslie (BJD 65 416 1953) In malignant melanoma (q v) such universal pigmentation is occasionally seen.

Lentigines are small, circumscribed, macular or papular lesions, brown to black in color Histologically one finds mainly intraepidermal changes, with melanin hyperpigmentation, chiefly of the basal cells, swelling of the rete cells in circumscribed areas and multiplication of the clear cells (q v) and loss of fibrillary structure Further evolution of these junctional nevoid changes results in cystlike spheres wherein typical nevus cells develop and drop off or descend into the dermis, so that in slightly raised lentigines, nests of nevus cells are found characteristically in the papillary layer (Zeisler and Becker ADS 36: 109 1936)

A lentigo is a nevus cell tumor of min te size and of early o bortive development. Lentigines are distinguished from ephelides (Brown: ADS 47: 804, 1943) by their appearance at an ea lie age approximating 2 years rather than 6 or 9 years, by their constancy

of number without regard to sunlight, by their disseminated distribution rather than predilection for exposed parts, by their presence in persons of any complexion and by their comparative smallness, discreteness permanence darkness of pigmentation, ability to enlarge and to become papular and potentiality for the development within them of malignant melanoma, though this is rare. Curious instances of their appearance in great profusion have been recorded (Zeisler and Becker 1936; Semman: BJD 61 289 1949) Occasionally they are arranged as a nevus unius lateris (ADS 43: 410, 1941; Cappon: BJD 60: 371 1948) Pigmented macules were seen on the chin neck and arms of 3 sisters in the form of small closely set, macular lesions, in some areas confluent, comprising a familial anomaly present since infancy (Becker and Reuter: ADS 40: 987, 1939) They also occur in xeroderma pigmentosum, hypoadrenal states and other conditions.

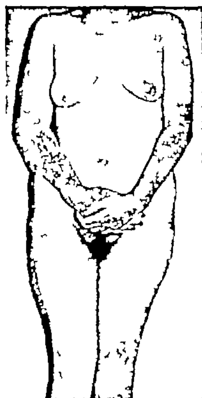


Fig 894 —Generalized lentigines in a girl with urticaria pigmentosa.



Fig 895.—Lentigines, forearm and arm, in case shown in Fig 894

To remove lentigines requires that at least some dermal tissue be destroyed hence at least some scar results, even if it consists only in permanent depigmentation of the small area. A lentigo or the scar resulting from its removal can be *hidden nicely by means of a cosmetic, such as* Spot Stick.

Lentigo Senilis is a name applicable to benign, discrete pigmentary macules developing on senile keratotic, xerotic or xerodermatous subjects (Cawley and Curtis ADS 62 635 1950) They sometimes evolve into keratoses and carcinomas Pigmented basal cell carcinoma may commence as a lesion clinically indistinguishable from a lentigo An occasional seborrheic keratosis is practically macular and can be blistered with the cautery and wiped off without leaving a trace of pigment. This cannot be done with lentigines for some of their pigment is within the dermis.

Malignant Lentigo Hutchinson s infective melanotic freckle, is a malignant melanoma macular in its early stage (see p 1089)

Freckles (Ephelides) are little circumscribed, brownish macules. Constituting a familiar pigmentary peculiarity they are usually seen in early adolescence and the depth of pigmentation as well as the number of visible lesions is greater during the sunny months. Usually they are less conspicuous during the winter many macules disappearing altogether Roentgen treat

ment of dermatoses often provokes intensification of pigmentation in these macular areas, where melanoblasts are numerous. They give rise to no symptoms and are harmless (see Brown ADS 47 804, 1943) They consist of collections of melanin pigment in the basal layer of the epidermis. An application of 25% phenol in ether followed by protective bland unguent dressings will peel them off according to Winter (BJD 62 83 1950)

Mongolian Spots are congenital bluish or brownish macular spots, generally occurring on the lower sacral areas, but sometimes on other parts of the body They are asymptomatic, and do not alter the texture of the skin by their presence. They may be single or grouped, and small or large. They may disappear after a few months, perhaps as a result of being hidden by deeper pigmentation of the surrounding normal skin, as noted by Metzger and Clarin (BullSocd obst. 23 442, 1934) Ashmead (JCutD 23 203 1905) considered them a primitive simian character Their presence seems not to have factual relationship with mixture of racial blood although the lesions are commoner in Mongolian and Negroid races than in the white (Edit J 115 2182, 1940)

Aberrant cases were reported by Cole et al. (ADS 61: 244, 1950) who noted that the light blue to grayish green lesions sometimes make their appearance afte birth and continue to spread for some years. The specific cells in them responsible for the pigmentation resemble those of the blue nevus but are scattered between connective and elastic tissue fibers parallel to the epidermis The Mongolian cell found in the lower part of the dermis is a long, fusiform cell, 5 to 10 μ wide and 25 to 75 μ long, often having several dendritic processes. The pigment i melanin, gives a positive dopa reaction, and may be seen in unstained specimens in the form of fine granules of light to dark yellowish brown throughout the cell. The same cells when densely accumulated constitute the blue nevus (see p. 108.)

The lesions were bluish, resembling bruises, and numerous, especially on the upper trunk, nd the conjunctivae were involved in the remarkable case of Carleton and Biggs (BJD 60: 10 1948) The distribution was limited to an extensive patch on the right side of the forehead in the girl described by Pariser and Beerman (ADS 59: 396 1949)

See Ahmed (AfDuS 141 171, 1932) in Europeans; Castellani and Chalmers (Tropical Medicine, Wood, 1919); Matus (SoAfrMJ 15 121, 1941) in Cape Negroes Piers (SoAfrMJ 23 210, 1949) on East Africans.

SYMPTOMATIC MELANOTIC HYPERPIGMENTATION

Symptomatic pigmentation may result from the local action of heat, pressure friction from truss pads and similar appliances, scratching provoked by pruritic disorders, actinic light (see contact photosensitization) x rays and chemical irritants. Brunets are able to produce deeper pigmentation than blonds. In the skin of brunets and Negroes most inflammatory processes activate visible local production of pigment. The lesions of pityriasis rosea furuncles, erythema multiforme drug eruptions pellagra, lichen planus, acne and the like do this. Months may pass before normal coloration is regained. Some dermatoses, such as lupus erythematosus and achromia parasitaria, lead to depigmentation.

A high-voltage television set was the source of x ray energy that produced pigmentation of the cheek, shoulder and arm of a Negro radio repairman presented at a 1955 meeting of the Kansas City Dermatological Society by Dr T B Hall

Spectrophotometric studies of pigmentation were made by Edwards and Duntley (Sci 90 235 1939; AmJAnat 65 1 1939) demonstrating as sources of skin color melanin a melanoid substance and carotene as well as reduced hemoglobin and oxyhemoglobin. Following solar irradiation the increase in melanin was apparent by the second day reached its maximum on the nineteenth and diminished slowly during the subsequent 9 months, by which time the skin had returned to normal.

In the Negro, the skin darkens a few hours after birth and the depth of melanosis gradually increases reaching a maximum at about the age of puberty thereafter diminishing (Lewis Biology of the Negro University of Chicago Press, 1942) There may be seen in some 15% of Negroes a definite

of number without regard to sunlight, by their disseminated distribution rather than predilection for exposed parts, by their presence in persons of any complexion and by their comparative smallness, discreteness permanence darkness of pigmentation, ability to enlarge and to become papular and potentiality for the development within them of malignant melanoma, though this is rare. Curious instances of their appearance in great profusion have been recorded (Zeisler and Becker 1936; Samman: BJD 61: 289 1949) Occasionally they are arranged as a nevus unius lateris (ADS 43: 410, 1941; Capponi: BJD 60: 371, 1948) Pigmented macules were seen on the chin neck and arms of 3 sisters in the form of small closely set, macular lesions, in some areas confluent, comprising a familial anomaly present since infancy (Becker and Reuter: ADS 40: 987 1939) They also occur in xeroderma pigmentosum, hypoadrenal states and other conditions.

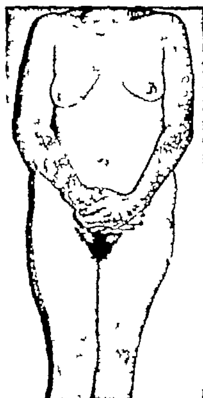


Fig 494.—Generalized lentigines in a girl with urticaria pigmentosa.



Fig. 495.—Lentigines, forearm and arm, in case shown in Fig. 494

To remove lentigines requires that at least some dermal tissue be destroyed hence at least some scar results, even if it consists only in permanent depigmentation of the small area. A lentigo or the scar resulting from its removal can be hidden nicely by means of a cosmetic such as Spot Stick.

Lentigo Senilis is a name applicable to benign, discrete pigmentary macules developing on senile keratotic xerotic or xerodermatous subjects (Cawley and Curtis ADS 62 635 1950) They sometimes evolve into keratoses and carcinomas. Pigmented basal cell carcinoma may commence as a lesion clinically indistinguishable from a lentigo An occasional seborrheic keratosis is practically macular and can be blistered with the cautery and wiped off without leaving a trace of pigment. This cannot be done with lentigines, for some of their pigment is within the dermis.

Malignant Lentigo, Hutchinson s infective melanotic freckle, is a malignant melanoma, macular in its early stage (see p 1069)

Freckles (Ephelides) are little, circumscribed, brownish macules Constituting a familiar pigmentary peculiarity they are usually seen in early adolescence, and the depth of pigmentation as well as the number of visible lesions is greater during the sunny months. Usually they are less conspicuous during the winter many macules disappearing altogether Roentgen treat

irregular patches symmetrically on the face and neck. The patches are reddish brown and are surmounted by fine, small, white adherent scales. The patients are usually women of menopausal age. Three stages were described by Joulia et al. (AnndeD 10: 364, 1950): first there are erythema, slight edema and itching then characteristic pigmentation starts around the hair follicles and extends over the face and neck; and finally the skin manifests dryness, desquamation and sometimes follicular hyperkeratosis. The disorder progresses irregularly in attacks and may progress to a stage of reticular atrophy with telangiectasia. Histologically the early phase shows some similarity to lichen planus.

See Hoffmann and Habermann (DMedWchr 44: 261, 1918) tar workers with Riehl syndrome and oil acne; Thibierge (AnndeD 6: 705, 1925) 42 cases, Riehl type; Graham-Little (BJD 32: 242, 1920), 2 cases of dyschromia of face; Kerl (ArDuS 130: 436, 1921) Riehl melanosis Barber (BJD 38: 295, 1926) case with histology; Graham-Little (BJD 40: 221, 1928) 9 cases and review, benefit with adrenal extract; Jausion et al. (BsocfrancD, Dec. 14, 1939) photodermatoses of war; Aria et al. (abs YBD 1940, p 304) review relation with photosensitization Friedman (ADS 41: 831, 1940) case Puente et al. (abs YBD 1941, p 512) 22 Argentine cases, Pierini (abs YBD 1941 p 504), various pigmentary abnormalities; Fernandes (abs YBD 1942, p 212) 10 cases; Jeghers (NEngJM 231: 88, 122, 181, 1944) complete review; Storck (Dermatologica 93: 346, 1946) 6 cases; Schwartz (ADS 56: 592, 1947), occupational melanoderma, Reiches (ADS 67: 616, 1953) 4 cases following occupational irritation by oily substances U bein and Ibees (abs BJD 65: 66, 1953) from benzanthrone.



Fig. 491.—Poikiloderma of Civatte. (Dr Robert N Andrade.)

Pseudoatrophoderma Colli is a rare pseudoatrophic disturbance involving the neck, observed by Becker and Muir (ADS 29: 62, 1934) in 2 otherwise healthy young women. The lesions were depigmented, macular and somewhat glossy and over them the epidermis was thrown up in tiny folds. The delicate wrinkling was eradicated temporarily by stretching the skin. Between the shiny macules the skin was dull and slightly scaly but textural difference was lacking. Micropathologic change was slight. A case was reported by Goldman and Taub er (BJD 50: 22, 1938). The 2 cases of Frost and Epstein (ADS 40: 755, 1939) in sisters, were parapsoriasiform. The back, chest and arms exhibited the disorder in the woman studied by Ayres (ADS 52: 280 1945). The cause is unknown, though it may represent endocrine imbalance. Vitamin A may help, Becker told me.

Pigmentation Due to Internal Disease may develop during the course of systemic disorders, debilitating or hypoendocrine, affecting the thyroid, gonads or adrenals. Pigmentation is characteristic of acanthosis nigricans (q v) and it is sometimes seen in prolonged wasting diseases such as tuberculosis, starvation, malaria, secondary syphilis, cirrhosis of the liver and cancer (Brunsting MedClinNoAm 21 861 1937). In Gaucher's disease subicteric pigmentation of exposed parts affects some 45% of the cases and in Niemann Pick's disease the skin is brownish yellow (Capper et al. AmJ MedSci 188 84 1934) see Xanthoma. Administration of *estrogen in various* conditions sometimes induces pigmentation sometimes cures it (Rocca JClinEndocrin 2: 217 1942). In pregnancy (q v) pigmentation is increased

over the whole body the nipples and areolae linea alba, pudendal regions and flexures are sites of greatest increase See Dermatologic aspects of endocrine diseases p. 692. Several varieties of dermatitis medicamentosa (q v) are associated with pigmentary changes fixed eruptions, arsenical pigmentation (diffuse as from small drops of rain) Atabrine gold silver (argyria)

See Costello (JMoMA 33: 82, 1936) tobacco-like stain on fingers of cretins; Degennes et al. (PresseM 44 37 1936) endocrine hepatocardiac syndrome, with cirrhosis, pigmentation, infantile stigmata, cardiac insufficiency. Klein (ADS 36: 267 1937), relation of nutrition and metabolism. Marchionini (ActaD-V 21 290 1940), in malaria. Gottron (ArDuS 181 171, 1940) senile acrogeria. Tolmach and Graham (ADS 46 1156, 194) in vitaminosis A. Herrnas (abs YBD 1944 p. 2) in asthma; Da is (JClinEndocrinol 6 128, 1946), from diethylstilbestrol g en for primary amenorrhea, reduced by giving chorionic gonadotropin Anderson (AOphth 38: 81, 1947) conjuncti al in hydroquinone workers Whitlock (ADS 64: 23, 1951) in cirrhosis of liver Costa (Dermatologica 105 166, 195) melanosis dorsalis, affecting upper back, as described by Arias and Pessano (PrensaMedArgent 26 2178, 1939) Moon-Adams and Slatkin (AD 1 691, 1955) symptomatic in dyskeratosis congenita. Gliston (OP 9 9 1955) Felty's syndrome; Clément (PresseM 63: 166, 1955) progeria.

Pigmentation of the Skin and Mucosae Associated With Intestinal Polyposis (Peutz-Jehgers Syndrome).—Pigmentation, usually in small patches on the mucosae of the lips, cheeks, gums and palate in the form of dark brown or black specks resembling freckles and sometimes on the skin near the nares and on the fingers and toes may be seen in patients with generalized intestinal polyposis (Peutz NederlMaandschrGeneesk 10 134, 1921 Jehgers NEngJM 231 88 1944 Jehgers et al NEngJM 241 993, 1031 1949) The cases reach hospital as a rule because of intussusception, and 2 such were reported by Walker Brash (BMJ 1 1132, 1954) If a young adult with this type of pigmentation suffers episodes of abdominal pain, cramping obstruction and perhaps rectal bleeding he probably has generalized intestinal polyposis (Bruwer et al. PSMMC 29 168 1954) The pigment is melanin.

See Jones (SoAfrMJ 27 938, 1953), 4 cases Crane and Light (BMJ 1 1132, 1954), 2 cases, Savage (BritJSurg 41 368 1954) case. Smith (BritJSurg 41 367 1954), case Lhe (J 155, 1462, 1954), résumé, bibliography Trozell (ADS 70 481, 1954) case Rankin and Laird (GlasgowMJ 35 ,54, 1954) 2 cases Curth (AD 71: 87 183, 1955) cases, pictures

Chloasma (Liver Spots) is the nonspecific designation of *melanotic* hyperpigmentation appearing as a rule symmetrically on the forehead and cheeks of persons whose metabolic derangements have resulted in symptomatic hyperpigmentation. The macular lesions are diffuse or discrete irregular and symptomatic They are sometimes coalescent. The only appreciable change in the skin is in its color In cases with diffuse pigmentation, involvement may be extensive and even universal. In the areas which are normally dark, such as the nipples, axillae and genitalia the coloration is exaggerated more than on other parts of the body The causes are various and include pregnancy (see p 703) chronic illness malnutrition, hypoproteinemia, avitaminosis and hypothyroidism. The café au lait spots of von Recklinghausen's disease and Mongolian spots are chloasma like but different.

Chl a ma bronzium wa described by Castellani and Chalmers (Tropical Medicine Wood, 1929 p 2232) as a rare affection, distinct from chloasma, occurring in both natives and Europeans in India, Ceylon, Malaya and China. Peculiar dark bronze discolorations ma klike may be seen on parts of the face or neck, occasionally on the whole of the face and on the neck and hest. Chron c recalcitrant unrelated to asthenia, malaria, argyria o ochronosis t may be expected graduall to fade when the individu l moves to a temperate climate

Erythrose Pigmentaire Péribuccale.—Diffuse brownish-red pigmentation about the mouth, chin, neck and perhaps the forehead, with or without slight burning sensation is seen in women of middle age Much of the color disappears on diascopy The disease is rare but clin cally distinctive first described by Brocq (PresseM 13: 62 1923). It is probably related to female hormonal influences, but is unresponsive to any known thera peut c measure The patient usually is in abundant health and complains only of the disfigurement (Ormsby and Ebert ADS 23 459, 1931) Cohen (BJD 60 203, 1948) gave a thorough review and suggested the administration of thyroid and estrogen.

Hypophyseal Cachexia (Simmonds Disease)—See Hypopituitarism p. 698.

Osteodystrophia Fibrosa.—See p. 1107

Werner's Syndrome.—See p 1055.

Felty's Syndrome.—See p. 1059.

Fanconi Syndrome.—See p. 1059

Treatment of Pigmentation Due to Internal Diseases.—As in all disorders of obscure origin, the patient with hyperpigmentation must receive thorough general examination. Remedies to be advised depend on the result thereof. Thyroid when needed works well. Pigmented patches can sometimes be temporarily removed by the use of various peeling solutions, such as 1% mercuric chloride in alcohol. This is painted on several times daily until mild desquamation results. The cosmetic "Covermark" may prove useful.

Depigmentation With Chemicals.—The monobenzyl ether of hydroquinone, a rubber antioxidant, is known to have caused occupational depigmentation. It is effectual by topical application in removing melanin hyperpigmentation (Denton et al. JID 18 119 1952 Lerner and Fitzpatrick J 152 577 1953) It did not influence melanin formation in vitro but given orally to guinea pigs it and related substances produced depigmentation. It specifically blocks the formation of melanin, perhaps at the dopa melanin



Fig. [illegible].—Chloasma which developed in an aged woman after influenza and which disappeared after thyroid was given with symptomatic benefit.

stage (Forman: BJD 65 406, 1953) A 20% preparation in a penetrant ointment base (Benoquin) while occasionally irritating or sensitizing may remove the discoloration of chloasma. Among the patients in whom I have found it satisfactory have been several Negroes darkened by x ray therapy

See Guy and Jacob (AD&S 40: 872, 1939) Oliver et al (J 113 927 1939) Schwartz et al. (PHRep 55 111, 1940), Oliver et al (AD&S 42: 993, 1940); Spencer (AD&S 58: 318, 1948), Berstein and Sachs (AD&S 59 542, 1949) Lockhart and Loewenthal (SoAfrMJ 23 887, 1949); Dotvinick (AD&S 62 334, 1950) from Rinette gloves McDonald (AD&S 61 [illegible], 1950) from stalite, an octylated diphenylamine; Schwatch (AD&S 63 785, 1951)

MELANOTIC HYPOPIGMENTATION

Loss of Melanin Pigment from the skin may be congenital or acquired. Albinism, complete or partial represents the former while vitiligo and secondary achromia exemplify the latter

Albinism is congenital achromia. It may be partial or universal. In partial (piebald) albinism, the lesions simulate those of vitiligo, but hyperpigmented areolae are not present. Rarely the lesions may be distributed as in nevus unius lateris. Hair in involved areas is white. In universal albinism the absence of melanin is complete. The pupil of the eye appears red and

the iris pink or bluish from reflected light and there are present more or less astigmatism photophobia and nystagmus The hair is white or pale yellow and is silky in texture The skin is whitish or pinkish in color and cannot tan on exposure to sunlight.

The incidence of albinism in the general population is in the vicinity of from 1 5 000 to 1 25 000 according to Fitzpatrick and Lerner (ADS 69 133 1954) who quoted Falls classification with modification

GENERALIZED ALBINISM: *complete* with hereditary recessive pattern, *incomplete* with some pigmentation in advancing age and recessive or irregularly dominant heredity and *albinoid-leukism* with light hair and skin but without nystagmus or photophobia.

LOCALIZED ALBINISM: *cutaneous*, with linear unilateral areas of depigmentation un changing throughout life and with dominant heredity; or *ocular* I which the whole eye or only the fundus is involved, in association with nystagmus, defective vision and head nodding



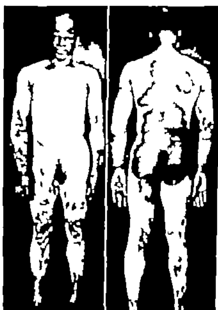


Fig 1000 —Negro, albino, uni volar twins (Wakefield and Dellinge AIntM 91 1149, 1918.)

F g 1001 —Piebald albinism, "The Leopard M n A hereditary dominant pigmentary anomaly (Keeler J 103 179 1934)



Fig 1002 —Vitiligoid nevus unius lateris no text ral change.

Melanocytes were demonstrated in albino skin by Becker et al. (ADS 65 511 1952) but tyrosinase has not been found The disorder appears to represent a genetic inability to convert tyrosine to melanin. With the exception *of the absence of pigment, the skin is normal in every respect,* although being sun-sensitive it is subject to the likelihood of development of keratoses and carcinomas (Curban J 148 1523 1952)

See Cockayne (Inherited Abnormalities of the Skin, Oxford University Press, 1933, p. 50) Loewenthal (ADS 50 300 1944), 3 Negroes also with congenital nystagmus; Kukita and Fitzpatrick (Sci 121: 893, 1955) absence of tyrosinase demonstrated by autoradiographic methods; Smith and Schulz (AD 71 486 1955) partial albinism, usually with white forelock, inherited as a Mendelian dominant in 4 generations.

White Forelock occasionally occurs as a sort of partial albinism, sometimes alone when it may be inherited as a dominant character and sometimes as the scalp manifestation of piebald albinism (Nussey Lancet 2 947 1938; Cooke J ediat 41 1 1952) See Canities (p 1346 and Fig 1844)

Vitiligo is acquired achromia. Milky white patches of various sizes and shapes develop generally sharply demarcated, irregularly oval in outline with hyperpigmented areolae. Their distribution is more or less symmetric, the dorsa of the hands sides of the neck, and trunk being sites of predilection but no region is exempt Involvement is sometimes almost universal (Twining ADS 41 444 1940) The activity of glands in affected areas is not influenced, but hair commonly loses its pigment The disease is irregular in its course sometimes spreading sometimes undergoing repigmentation spontaneously The hair follicle is the last region from which pigment is lost when it is on the way out and the first site of repigmentation when this takes place The lesions are asymptomatic and are not significant of consequential



Fig 1003—Mottled depigmentation secondary to chronic lichenoid dermatitis (Dr O. G Costa)
Fig. 1004—Vitiligo.
Fig 1005—Vitiligo in full-blooded American Indian (Dr Everett S. Lain.)

systemic disorder They are more apparent when the skin is illuminated with ultraviolet light (Bommer DWchn 98 43 1934)

The cause is not known The only histologic abnormality is absence of melanin and melanocytes in the lesions noted Bloch (MfDuS 124 209 1917) A Negro treated for thyrotoxicosis with thiouracil developed vitiligo (Lerner and Fitzpatrick PhysiolRev 30 91 1950) It is occasionally familial (Jaenicke ADS 48 519 1943) and sometimes accompanies alopecia areata. When full thickness grafts were exchanged experimentally the normal graft retained its pigment and the vitiliginous skin remained depigmented (Spencer 64 514 1951)

Treatment that is dependable has not as yet been devised. The average patient is correctly advised that the disease does him no harm, and does not

indicate anything importantly wrong with his bodily economy and that it should be lived with rather than fought with.

A skillful cosmetician can compound preparations which hide disfiguring lesions quite successfully. These may contain Bismarck brown, henna and carmine. Walnut juice (fluidextract of *Juglans nigra*) can be used to stain the areas pleasantly. The borders of the lesions are contrastingly hyperpigmented; this can be reduced by cleverly applying 1% alcoholic solution of $HgCl_2$.

It was noted by Schamberg (ADS 18: 862 1928) that a greenish blue or mauve tattoo results from inadvertent extravascular injections of gold sodium thiosulfate into the skin. Gold was injected intradermally in order to induce repigmentation by Yong (ActaD-V 21: 657 1940). Hathaway (ADS 52 117 1945) gave B complex and HCl with occasional improvement and without harm to the patient. Reinhauer (ADS 49: 13-, 1944) reported para aminobenzoic acid ineffectual. Although intradermal injections of tyrosinase into normal skin induced widening pigmentation about the site vitiliginous areas did not respond (Sharlit: ADS 48 111 1943) nor could such areas be ind ced to undergo pigmentation by the therapeutic production of contact photosensitization (p. 14)





Fig. 1006.—Vitiligo.
Fig. 1007.—Nails depigmented within vitiliginous areas. (Dr O G Costa.)

Intravenous injections of gold salts (Lindsay: ADS 20 22, 1929) I judge to be unjustifiably hazardous. Van Studdiford injected bismuth into Negroes with vitiligo and after prolonged treatment obtained considerable repigmentation, but it remai ed partial. Oral Bistrimate helped cases of Howles (SouthMJ 41 1033, 1948). The use of a m lanotropic pitu tary hormone by Fournier et al. (JClinEndocrin 3: 333, 1943) is of the ret c interest.

Chemical substances isolated from the fruits of the Egyptian plant *Am i majus* L. a by Fahmy and Shady (JPharm 21: 449 1948) were tried by El Mofti (JRoyEgPtMA 31 651 1948) and reported to promote repigmentation i vitiligo. Sekla (ADS 64: 796, 1951) discussed the t eatment before the N w Yo k Academ of Medici e on Feb. 7 1950 arousing keen interest among the dermatologists of the United States. The active ingredients he said are ammoidin and ammidin, and he (ADS 63: 338 1951) gave further details regarding the simultaneous oral and internal administration of the substances. The technic of treatment was elaborated by El Mofti (BJD 64: 431 1952). According to Sidi and Bourgeo s Ga ardin (JID 18 391 1952 PresseM 61 436 1953), the powder of the plant was used as early as the Thirteenth Ce tury by Egyptia fo the treatment of vitiligo, for it aduces photosensiti ation a d acti ates pigment formation, but it use is not free from side effects. The crystallin bitter extract ammoidin and ammidin are related to furocoumarin. They were identified psoralen derivatives by Lerner et al. (JID 20 299 1953) ammoidin being identical with xanthotoxin, majudin with bergapten, and amidin with imperatorin. Psoralens have been obtained from a numbe of plants, including bergamot, and ccount for the hyperpigme tation of berloque dermatitis. Ammoidin (8-methoxypsoralen) in solution does not affect the tyrosinase system or influence

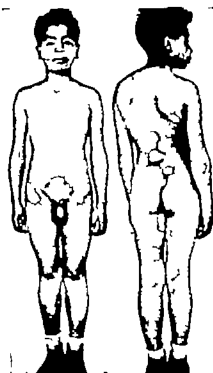




Fig. 1008.—Vitiligo. (Dr Robert N Andrade.)
Fig. 1009.—Extensive vitiligo in a Negress (Dr J Lamar Callaway)





Figs. 1010 and 1011.—Vitiligo affecting penis and vulva. (Dr O G. Costa.)

histochemical tests for tyrosine activity Lerner et al. stated. Since oil of bergamot was tried for years and found wanting I suspect that the derivatives of *Ammi majus* will likewise prove disappointing The results of treatment generally include marked pigmentation at the edges of lesions and irregular and unsatisfactory repigmentation within the areas. Nausea, insomnia, hepatitis and nephritis have followed its administration. Ultraviolet irradiation, a necessary part of the treatment must be given with caution to a patient who has been rendered photosensitive purposely (Sidi and Bourgeois-Gavardin: PresseM 61: 436, 1953) Cases exemplifying partial repigmentation were presented by Wolf (ADS 67: 333, 1953) Fairly good results were claimed by George and Burks (AD 71: 14 1953) who used an ointment alone or in combination with oral administration in 11 Negro patients. Good cosmetic results were obtained in only 6 of 85 cases treated by Kanof (JID 4 5 1955) I have never prescribed ammoidin or ammidin.

See Montgomery (ADS 34 873 1936) lips involved, mustache used to protect sun sensitive skin Shaffer (JID 1: 225, 1938) copper useless Oliver and Tobin (ADS 39: 664, 1939), gold dermatitis followed by partial repigmentation Lerie (UCutRev 46 34 1942) familial vitiligo Rothman et al. (ADS 48: 409 1943) iron by electrophoresis stains por area in normal skin, not in vitiliginous Costa (BJD 59 104 1947) Brazilian cases.

Vogt-Koyanagi Syndrome.—The conspicuous symptoms are nontraumatic bilateral uveitis, premature graying of the hair alopecia, symmetric vitiligo especially on the hands, wrists and feet and dysacousia. The patient complains also of great fatigability, which was thought to represent hypothyroidism by Parker (AOphth 4 439 1940) The syndrome develops most frequently in Japanese subjects of from 30 to 40 years of age (Durand BolAsocMédPuertoRico 35: 218 1943) Lewis and Esplin (ADS 50 626, 1949) reported a case and reviewed the literature The patients may or may not recover

See Alopecia areata also Zentmayer (AOphth 27 342, 1942) case Carrasquillo (AOphth 28 485, 1942) poliosis in 82%, vitiligo in 62%, alopecia in 53% dysacousia in 50%, hyperesthesia to noise tinnitus, partial or complete deafness Olvner (AOphth 30, 331, 1943) association with retinal detachment, recovery Hague (AOphth 31 520, 1944) Bahrman et al. (ADS 67 226, 1948) case, with 700 lymphocytes in CSF virus not found (Rosen AOphthalmol 33 281 1945) 47 cases, poliosis in 90%, alopecia in 73%, vitiligo in 63% deafness in 34% Robinson (BMJ 2: 792, 1954) case.

Secondary Depigmentation follows various scarring disorders, such as lupus erythematosus. Scars of syphilis are often mottled. Burns and scalds may remove pigment permanently although radiant heat usually increases it The occupational trauma incident to trumpet playing caused depigmentation of upper lip areas in the Negro musicians described by Freeman and Hazen (ADS 48 605 1943) A Negro with vitiligo who determined to be all white, scraped palm size areas, applied tincture of iodine, and obtained cosmetically satisfactory superficial, depigmented scars (Guy and Jacob ADS 40 672, 1939) See pityriasis simplex faciei (p 898)

Consecutive Achromia is the symptomatic loss of pigment resulting from such dermatoses as tinea versicolor, syphilis, pinta, psoriasis lichen simplex, lupus erythematosus and leprosy (Niles ADS 29 240 1934) The vitiliginous leprid is incompletely achromic and is thermoanalgesic (Urueña ADS 97 4?0 1933)

The skins of some Negro workers were bleached without inflammation by the hydroquinone antioxidant of their rubber gloves (Oliver et al.: J 113 9?7 1939; Schwartz et al. PHRpt 55 1111 1940) Hairs were not depigmented. Repigmentation eventually followed withdrawal from contact with the chemical Agerite alba. See Depigmentation from chemical (p. 703)

Pseudoachromia Parasitica is characterized by actinic hyperpigmentation of normal skin about the more or less circular macules of tinea versicolor (q v) The areas of infection are pale because the fungus is relatively opaque though the sunburn which hyperpigments the normal skin may desquamate and cure the disease See p. 514.

Vitiligo With Raised Borders is occasionally seen (Garb and Wise: ADS 58: 149 1948 Buckley and Lobitz: ADS 67: 316, 1953) While the depigmentation closely resembles that of vitiligo, the edge is elevated, inflammatory and pruritic, leaving depigmentation without atrophy inside its slowly advancing margin. Scrapings from the marginal dermatitis show fungi on examination in potassium hydroxide but I have not been able to cultivate the organism, which resembles that of tinea versicolor *Fungicidal* medication cures the dermatitis, but depigmentation remains for a long time.

INCONTINENTIA PIGMENTI

Symptoms.—The first recorded case of this rare, peculiar dermatosis was that of Bloch (SchweizMWchn 56 404 1926) studied also by Sulzberger (AfDuS 154 19 1928) who was able to collate data on this patient and 3 others, familial, seen by Naegeli. Incontinentia pigmenti was the name

preferred by Sulzberger et al. (ADS 38 57 1938) in their collation of 8 instances of the disorder showing the characteristic manifestation of pigmentation distributed in macular areas of bizarre irregularity with sharp jagged outlines, disseminated over the trunk and extremities but not zosteriform or definitely systematized. The color is tan brownish or slaty The lesions of their patient were unilateral and were associated with familial ectodermal defects.

The onset of cutaneous abnormality is early perhaps even at birth. The pigmentary dystrophy in some cases is preceded by bullous and lichenoid dermatitis (Heilesen ActaD-V 28 544 1948) Haber (BMJ 2: 230 1949) in

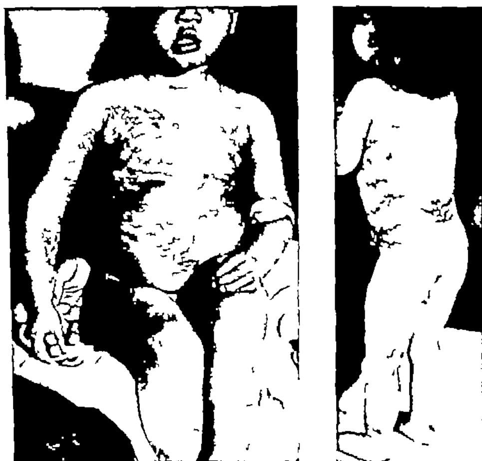


Fig. 1012.—Incontinentia pigmenti. (Hopkins and Machacek ADS 43 728 1941.)
Fig. 1013.—Incontinentia pigmenti. (Epstein et al. ADS 65 557 1952.)

presenting 3 cases, stated that the presence of a vesicular eruption at birth preceding the linear depigmentation is characteristic A patient of his (BJD 61 104, 1949) was born with lesions on the right arm which became generalized on the fourth day A later stage of hyperkeratosis follows, simulating an epithelial nevus. The disease becomes classic in its third and final stage The macular or diffuse erythema which is present at or soon after birth is associated with lichenoid papules and bullae arranged irregularly or in stripes, stated Findlay (BJD 64 141 1952) and this condition is soon replaced by typical incontinentia pigmenti, the transition being not easy to follow because most case reports are concerned with the appearance of the patient after the originating dermatosis has completely disappeared.

The syndrome in its full development includes the overlapping stages of vesicular dermatitis, hypertrophy and pigmentation (Epstein et al. ADS 65 557 1952) Of 29 cases reviewed by Franklin (BMJ 1 75 1952) 26 were females skin lesions were present at birth in 11 and pigment abnormality was present at birth in 2. Some kind of congenital defect of the eye was present

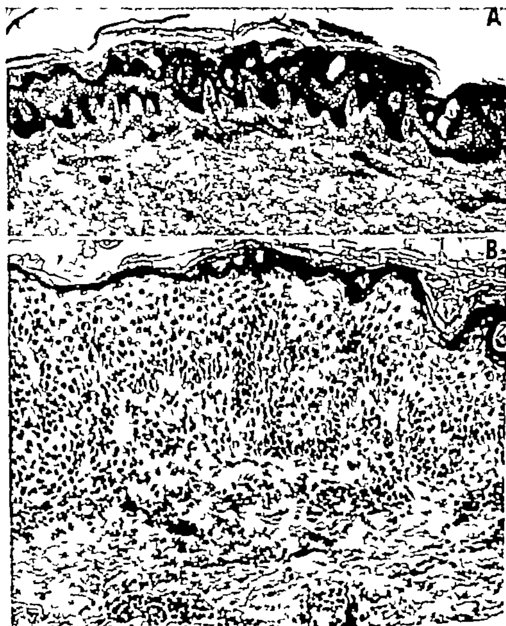


Fig 1014 — Persistent disturbance of keratinization and incontinentia pigmenti at age of 1 year. A, above, shows acanthosis, hyperkeratosis and intraepidermal centers of keratinization, which often simulate sweat ducts; mild perivascular infiltrate and melanophores in the upper dermis. B below shows high-power view of a section similar to A with irregularity of basal layer and some invasion of epidermis by inflammatory cells, dyskeratotic cells and whorls in the epidermis, and heavy pigment deposits in the subpapillary layer. (Drs. Stephen Epstein, J B Vedder and Hermann Pinkus.)

in 6 of the 29 and other defects were noted, including abnormalities of the nails patchy alopecia dental hypoplasia, congenital heart disease and even congenital blindness.

Pathology — In the initial stage of vesiculation, tense intraepidermal vesicles were described by Carney (ADS 64 126 1951) the fluid content being rich in eosinophilic poly-

morphonuclear leucocytes. Epidermal pigmentation was not conspicuously altered. Melanophores were found in the cutis in large numbers, and mild inflammatory changes were seen in the superficial dermal tissues. The dopa reaction in the cutis was negative and no formation of pigment was there demonstrable. This distinguished the lesions from those of blue nevus or Mongolian spots. The pathologic findings were interpreted by Sulzberger et al. (1933) to indicate that melanin in the epidermis had descended into the cutis in a manner suggestive of autochthonous tattooing Histologic resemblance to lentigo was noted by Crawford and Damiana (ADS 60: 926 1949)

Etiology and Treatment are unknown. Inflammatory erythema, vesiculation and crusting were the initial lesions in 3 cases of Doornink (Dermatologica 102 63 1951) who thought the phenomenon of pigment loss is not a specific entity but a form of consecutive achromia. The pigmentary stage persists for a number of years, but tends eventually to fade. The syndrome disappeared in the 3 cases of Loveman et al. (JPediat 40 442, 1952)

See Siemens (AfDuS 157 382, 1929) case; Cockayne (Inherited Abnormalities of the Skin, Oxford University Press, 1933, p. 325); Scheermann (DWchn 109: 979 1930), case; Hopkins and Machacek (ADS 43 733 1941, case in Negroes; Carol and Roor (abs ADS 46 775, 1942) case; Skeer (ADS 41 148, 1940) girl 14, lesions of 4 years' duration Pierini et L (RevArgentD 29, 161 1945), eleventh case female infant; Sobel (ADS 53 467, 1946) Chinese female Sulzberger and Bloom (ADS 58; 468, 1948) case; Kümer and Keisel (Ztsch Kinderh 66; 411, 1949) case Carney (ADS 64: 176, 1951 BJD 64 201, 1952) in sisters, pigmentary macules re often preceded by inflammatory lesions, Miller (ADS 65 263, 1952) case; Haber (BJD 64 129 1952), 3 cases, review; Rein and Wendas (ADS 65: 361, 1952) case; Kitamura et al. (ADS 69: 667 1954) 3 original and 13 other Japanese cases Murray Will (AustralJD 2: 140, 1954) bullous lesions in early stages, or linea verrucous lesions, disappearing to leave pigmented macules, Philpott et al. (AD 71 214 1955) 4 cases, 7 familial; Cramer and Schmidt (AD 71 699 1955), 6 cases, earliest stages neonatal, with eosinophilia and bullae usually; Schamberg et al. (AD 72: 304, 1955) case, bullous onset.

STAINS

Discoloration of the skin due to staining can often be removed by washing with a solution of potassium permanganate followed by washing with a solution of sodium bisulfite one may actually rub the skin with crystals of the latter after which the skin is thoroughly rinsed (Tuckerman J 136 643 1948) For permanganate stains, a mixture of cream of tartar and H O is effective (Morgan and Balyeat ADS 69 104 1954); a paste of baking soda and water will clean stained fingernails.

A stain, such as that caused by silver nitrate, will be lost in due time by physiologic exfoliation Silver staining can be removed by 10% KI by a mixture of 10% HgCl and 10% NH_4Cl, or by a mixture of 1% potassium ferricyanide and 6% sodium thiosulfate (QMN J 157: 782, 1955) Sodium thiosulfate removes iodine stains even from starched clothing Removal of stains was discussed by Cornbleet (J 135: 573 1947) See also Chromhidrosis, and Discolorations of the nails.

The mechanical irritation produced by too vigorous washing or by washing with irritating chemicals is commonplace in the practitioner's experience. Many a case of dermatitis is attributed by the patient to a staining substance— ditto ink, for example—when it is actually due to the methods used for cleansing See Dermatitis venenata.

Pigmentation not due to transitory superficial discoloration may be caused by nonautochthonous substances which have entered the skin from within the body as from Atabrine or in argyria, or which have entered the skin from without, as in tattoo.

TATTOO AND POWDER STAINS

Tattoo results when there are introduced into the dermis insoluble substances such as carmine cinnabar indigo and carbon. Infection with syphilis, tuberculosis, leprosy verrucae and other diseases may be inoculated by the use of dirty tattooing needles. The coloring matter rests within the connective tissues surrounded by a fixed tissue foreign body reaction (Bettley BJD 52 129 1940) without being removed by phagocytosis, so that it is indelible permanent and removable only by procedures which produce scars.

Accidental tattooing is seen following powder burns, excoriations or lacerations which introduce carbon into the skin. The miner (Lewin DZtschr

73 135, 1936) and the soldier are occupationally subject to this. Tattoo may result from lead pencil injuries accidentally or intentionally made by children from the medicinal use of ferric chloride (copperas) from a mercury containing bleaching cream (Goeckerman J 79 605 1922 84 506 1925) and from gentian violet used in the treatment of ulcers (Sutton J 110 1733, 1938) The presence of mercury in the skin resulting from the use of a face cream was proved by Hollander and Baer (ADS 20 27 1929) who were able to induce the gray duskiness to fade by applying tincture of iodine followed by alcohol so dissolving away mercuric iodide they thought.



Fig 1015 —The late Professor Gus Wagner tattoo artist and loyal friend. (With permission.)



Fig. 1016 —Gentian violet tattoo, following use of th dye in treating a granulating wound. (Sutton J 110 1733 1938.)

Chronic mercurial dermatitis has been observed in tattoo (Madden: ADS 33: 451 1939; MacDonald J 114 1491, 1940; Wolff and Sidell: ADS 69: 625, 1934) In similar cases of Unna (AfDuS 160 153, 1930) and Ballin (ADS 27: 292, 1933) patch tests with mercury w re positive Belote (ADS 28 200 1923) noted that syphilitic lesions shun the regions of tattooed figures which re pigmented red with a mercury salt.

Charcoal applied as a medi al agent tattooed the scar of n ulcer on a man leg (Drant ADS 34 37 1936) Blue trophy du to injections of snow by addicts was described by Gottheil (JC AD 30 1 191?) While o e might expect bluish tattoo to result from flaming th needl before ts introduction into the skin, the patients seen with this rare cond t on den ed ch aseptic technic. The usual result of morphine addiction is not tattoo, although it m y be k loid (q.v.) Rust o the carbon from flaming the needle may howeve t ttoo the victim (Wright and Friedman: ADS 40 630, 1939).

Foreign body reaction in the form of a benign tumor may result from tattooing (Madden: ADS 40 536 1939) Sa coid developed in a tattoo observed by Oberm ver and Hassen (AD 71: 60, 1955)

A patient of Madden (ADS 60: 789 1949) developed lupus erythematosus in the red part of his tattoo 4 years after it was done. Similar cases were seen by Hall (ADS 47: 610 1943) and Rook and Thomas (DJD 64: 62, 195)

Tattooing as a method of treatment has been discussed in connection with pruritus ani (q.v) As an adjunct to plastic surgery tattoo may be used to improve the color of a graft, to simulate beard stubble or eyebrows (Matthews: ProcRoySocM 40: 851, 1947) o to hide a birthmark (Conway and Doktor: SGO 84: 666, 194)



Fig. 1017.—Iron stains of dermis following applications of copperas a a home remedy for im petigo. The pigmentation eventually disappeared. (Sutton J 108 112, 1937)

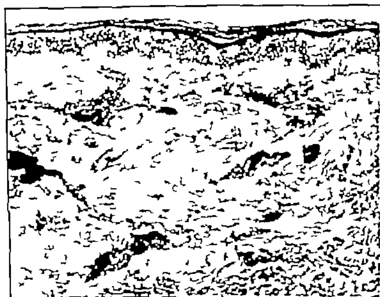


Fig. 1018.—Tattooed skin, showing location of coloring matter (Dr George H. Belote.)

Leprosy was inoculat d into individuals on the same day by a Melbourne artist, and maculoanesthetic lesions made their ppearance in the tattoos about 30 months late (Porritt and Olsen AmJPath 23: 803 1947)

Iron Deposits in the Cutis sometimes result from the pplication of an iron salt, usually copperas, to an exudati e dermatitis. The brown stain is presumably a basic ferrous e tate or simila organic combination ttached to the collagen in a relativel permanent way (Sutton J 108: 112, 1937) The tattoo accurately outlines the previously exudative areas with sharp margination and it is generally a bit deeper in color at the periphery Sometimes the discoloration can be removed by ultraviolet o cantharides blistering It disappears spontaneously afte a few years (Straus ADS 55: 692, 1947)

Iron salts have been applied far more often than they have caused pigmentation. It seems that the mordant action of a weak organic acid is simultaneously requisite, such as might be supplied by the concurrent use of aluminum acetate or the carbonate in calamine lotion.

Methods of Removal of Tattoo are surgical, electrolytic and chemical. Long narrow marks may be excised. The superficial layers may be shaved off by means of the dermatome and the area may or may not require covering by grafting Minute specks of powder stains can be removed by the negative galvanic needle or dug out by a small sharp curet They should be removed at the earliest possible moment, and this can be done by scrubbing the skin immediately after its injury with a sterile brush. The cutaneous punch in common use today was devised by Keyes (JCutD 5 99 1887) for the purpose of removing powder stains from the face of a boy injured by fireworks. An effort can be made to hide unsightly powder marks by tattooing flesh-colored pigment over them. One can protect the border with petrolatum, moisten the skin with strong tannic acid solution, needle the design, rub it with silver nitrate stick cover it with powdered tannin, and await the slough. Abrasion as a method of treatment has a long history anesthesia, scrubbing with a rasp and massage of the denuded area with salt crystals was recommended by Janson (DWchn 101 894 1935) and the effectiveness of the method was attested by Klövekorn (DWchn 101 1271 1935) Crystals of $KMnO_4$ may be so used. I have tried to rub off lesions with sandpaper as recommended by Rostenberg (ADS 65 466 1952) and Strakosch (ADS 67 53 1953) and have not been satisfied with results (see also Acne treatment) I find it possible in treating relatively small areas, to destroy by means of the actual cautery under local anesthesia just the right amount of dermis so that the superficial one third of the cutis sloughs off carrying with it the unwanted pigment and resulting in an acceptable flexible smooth scar Electrocoagulation was so used by Belot et al. (BSocfrançD 46 315 1939) There is little doubt that plastic surgery utilizing the dermatome generally does the best job.

See Watson (MRec 14 78, 1878) discotome, Variot (JCut&VD 7 [illegible], 188[illegible]) tannin and silver nitrate Dubreuilh (AnndeD 10 347 1908) shave and graft Dohi (ADerm 94: 3 1909) histology Pusey (J 68 637 1917) copperas Butler (JCutD 35 116, 1917) copperas Keidel and Zimmermann (AmJSyph 2 41, 1918) tattoo and syphilis Mellon (BJD 34 221, 1922) inoculation of verrucae, Muller (AmJSurg 10 [illegible], 1925) excision Hambley (The History of Tattooing and Its Significance, Witherby 1926), 346-page monograph Cohen (BJD 39: 390 1927), psychology of tattooing Ihle (J 84: 34, 1925) review preference for Variot's method Scheinberg (ADS 18 862, 1928) intradermal gold extravasation producing tattoo, Pototski (DWchn 101 847 1935) zinc escharotic for removal; Traub and Tennen (J 106 1711, 1936), ferric chloride used in treatment of poison ivy causing iron stain Karpelis (MuenchMWchn 184 [illegible] 1937) excision best; Lindsay (J 109 1530, 1937), eye curet to pick out grains in powder stain, Becker and Bienhoover (ADS 37 920, 1938) copperas, QAIN (J 110 2140, 1938) removal, Bloom (ADS 41 819, 1940) electrodesiccation removal Phillips and Kerr (ADS 41 964, 1940), copperas on poison ivy Kaufman (OhioMJ 37 234 1941) dental burr for powder burn; Rubetnat (ArchPath 31 646, 1941) correlation of tattoo and syphilis; Weiss et al. (ADS 43: 444 1941) iron deposit from ferrous sulfate and lead acetate used on poison ivy, Sulzberger et al (USNMB 43 883, 1944) desensitization to mercury Philip and Bayer (USNavMB [illegible] 442, 1947) Variot's method in 72 cases McKenna (Pract 160 471 1948) allergy to tattoo; Lerner (NYSJM 48 1937 1948) removal, Smith (J 144 1074, 1950) inoculation of infectious hepatitis Rostenberg et al (ADS 62 540 1950) ill effects classed as accidents incident to tattooing, results of introduction of foreign substances and transmission of infection, review; Lehr (DWchn 134 317, 1951) use of dental burr Hare (BJD 63 41, 1951) occupational exposure to iron Horsford and Smith (J 150 1482, 1952) fluorescein contact [illegible] violet Hobson et al. (BMJ 1 1111 1952), viral hepatitis transmitted Post (ADS 66 [illegible] 1952) lupus vulgaris developing at site Crawford (BMJ 1 948, 1953) abrasive and graft treatment

DERMATOSES OF NEUROLOGIC AND PSYCHIATRIC ORIGIN

ABNORMALITIES OF SENSATION

Paresthesia is abnormal sensation, such as burning prickling numbness or formication. It is of neuropsychiatric import, the dermatologist rarely being competent to specify its significance. It may occur in occlusive peripheral vascular diseases. A type of unknown cause is characterized by widely disseminated discrete areas where itching tingling and crawling sensations are experienced and the patient is led to believe himself, or more often herself, to be infested with parasites. Many cases of this sort are labeled acarophobia (q v) It is usual for these cases to be obscured by dermatitis venenata due to medicinally applied irritants. Large doses of vitamin A may relieve an underlying lichen spinulosus. High protein diet and injections of vitamin B_{12} are sometimes helpful. When paresthesia is central in origin, as it may be in arteriosclerotic disease of the nervous system Benadryl may be welcome in palliation. See also Tabes dorsalis (p 421) and ischemia (p 768)

Burning of the soles was noted in experimentally induced vitamin B_1 deficiency by Jolliffe et al. (AmJMedSci 198: 198, 1939) A syndrome of painful, burning feet observed among J panese prisoners of wa resembled erythromelalgia or causalgia, and vibratory stimulation would incite attacks of pain (Vernon: J 143: 799 1950) Usually cheilosis and scrotal dermatitis were present, and the syndrome appeared to be due to nutritional deficiencies (q v)

An encephalopathy seen in prisoners of war in Singapore, described by Graves (BMJ 1: 253, 1947) was characterized by spastic paraplegia of variable severity It began with locomotor disability weakness, stiffness, unsteadiness, and failure of vision. Paresthesias of the feet, with pain in the feet and back, were noted. Cramps, nocturnal incontinence, and depression or dulling of ment l function were further features. The onset and progress were fairly rapid, and many patients died. In those who recovered, residual symptoms ranged from none at all to disabling spastic paraplegia.

Itchy Points in the Skin is a rare disorder which has been confused with neurotic excoriation. No objective indication of bnormality exists unless this be excoriations. Itching is sharply localized to one or a f w pinhead size sites always discrete, usually overlying a bony prominence. The nature and cause of the disease are unknown (Toomey: AIDS 5: 744 1922) On might try removing the skin t the specified spot with a punch. Compare delusion of parasitism (p. 823) and one keratosa (p. 677)

Acroparesthesia is common during the menopause according to Goldberg (AmJObGyn 31: 161, 1936) the women complaining of numbness, coldness, tingling and crawling sensations, and they obtain relief on estrogenic therapy

Hyperesthesia is a functional disorder characterized by exaggerated sensitiveness of the affected part. The condition is symptomatic. The distribution may be universal but is generally localized. It may be unilateral or bilateral and transient or persistent, the duration depending on the underlying cause. Hyperesthesia may be due to inflammation of a viscus of the same segmental innervation as that area of the skin in which the symptom appears, as in appendicitis or salpingitis (Labate: SGO 65 321, 1937) Hyperesthesia may be caused by excess of caffeine and fatigue. Fright or anxiety may be causative (Kretschmer BMJ 2 574, 1937) It occurs as a symptom in influenza, dengue, tabes dorsalis, the pink disease ischemic neuritis, peripheral vascular diseases, trigeminal neuralgia, and neuritis following herpes zoster

Hypoesthesia, decreased sensibility of the skin, occurs in hysteria, neuritis, lepra and neural disorders such as spinal cord lesions and occlusive peripheral vascular disease. A pincushion man was interestingly described by Critchley (BMJ 2 891, 1934) Such individuals undergo severe injuries without giving evidence of experiencing pain (Ford and Wilkins BullJHH 62:

448, 1938) The patients appear to recognize the existence of the sensation, but are indifferent to it Analogy to color blindness was as much explanation as the authors could offer after 5 years observation of the patients, who were otherwise normal, disregarding the deformities caused by broken bones of which they had not apprised the parents (see p 30)

Dermatalgia is pain in the skin, not consequent to any appreciable structural lesion. The disorder is usually secondary to hysteria or some organic disturbance of the nerve centers especially the cord. Localized areas, particularly on the hairy parts, are affected It is frequent in tabes, and is occasionally met in diabetes mellitus.

Segmental Neuralgia, with hyperesthesia and often tenderness tingling sticking and burning sensations limited to sharply defined areas, is of fairly common occurrence It is probably an abortive form of herpes (Davis J 107 1620 1936) It is often responsive to therapeutic intracutaneous injection of vaccinia virus.

MERALGIA PARESTHETICA

Meralgia paresthetica affects particularly the outer side of the lower two-thirds of the thigh, which is supplied by the external femoral cutaneous nerve (White JCutD 24 160 1906) It is characterized by hyperesthesia or anesthesia and sensations of pain, numbness and formication. Severance of the nerve is therapeutically effective (Lee InternatClin 1 210 1936) The disease is usually unilateral, neither side predominating While it is bilateral in some 22% it begins unilaterally (Ecker and Woltman J 110 1650 1938) Numbness is the commonest and usually the earliest symptom It is constant. Tingling pain and burning occur only after prolonged standing upright. The syndrome first described by Bernhardt (NeurolCentralbl 14 242, 1895) may be the first sign of neurosyphilis or of an intraspinal or vertebral organic lesion. Many of the cases are due to trauma or pressure from orthopedic belts in men or from pregnancy in women (QMN J 110 148 1938) Involvement of the genitofemoral nerve was recognized by Magee (CanadMAJ 46 326, 1942) and followed appendectomy in 5 of his 7 cases. He obtained cures by resecting the nerve

Cheiralgia paresthetica involving the superficial branch of the radial nerve at the wrist was ascribed in one case to a wristwatch band (Wartenberg ZtschrNeurPsych 141 145 1932)

CAUSALGIA

Causalgia is a neuralgia featuring burning pain of a sort that is tolerable until the patient is touched, becoming far worse if the patient who dreads it, is touched It is due perhaps to nerve ischemia (see Glossy skin p 807) It occurred in a case of arterial embolism described by Homans (NEngJM 222 870 1940) It usually results from peripheral nerve injury and is associated with trophic and secretory phenomena Most often affected are the median nerve the tibial portion of the sciatic and, to a lesser extent the ulnar nerve noted Karnosh (JNervMentDis 84 283 1936) his 2 cases suggested the etiologic factor of damage to the blood supply of the nerve

Gunshot wounds of the extremities were causative in the 8 cases of Fuchs (abs J 119 982 1942) in which the typical features were present pain which (1) burns, pierces draws and tears (2) is not relieved by analgesics and (3) is elicited by tactile irritation of the involved area also (4) occurrence of synesthesialgia manifested by pain in one extremity on touching the other (5) pain elicited by sensory stimuli such as intense light or noises (6) transformation of psychic experiences into pain sensations such as origination of pain by anticipation of being touched (7) xerostalgia, i e pain incited by touching a dry or rough object (8) the patient tries to avoid excitation of pain by wetting stockings, gloves or skin or applying petrolatum (9) pain on movement and (10) algogenic or algophobic akinesia.

When the brachial plexus is affected, the fingers are usually tapering, smooth, hair less, almost devoid of wrinkles, glossy pink, ruddy or blotched as if with permanent chil blains, and the intensity of suffering varies from the most trivial burning to a state of torture which can hardly be credited but reacts on the whole economy until the general health is seriously affected. Exposure to the air is avoided by the patient with a care which seems absurd, and most of the bad cases keep the hand constantly wet. The patient walks carefully carries the limb tenderly with the sound hand, is tremulous, nervous and has all expedients fo lessening his pain (Speigel and Milowski J 1*7 9 1945) The symptoms can develop without blood vessel damage.

The sensory deficit does not necessarily outline the area of causalgia. Percussion of the involved nerv at the site of injury caused tingling in its distribution but no change in the pain. Disuse decalcification of the extremity develops, and immobilization by the patie t may even result in pressure sores.

Sympathectomy may relieve pain, but it must be complete and should not be per formed unless preliminary procaine block indicates its probability of success (Ulmer and Mayfield SGO 83: 789 1946) The pain path is in Lewis nocifensor system, and pain originates peripherally; it may persist o return after chordotomy or afte section of posterior roots depending o which severs the main pathway via the sympathetic chain to thoracic cord segment or via the posterio root of the I jured nerve (Bingham BMJ 2: 334, 1948)

Among 737 cases of peripheral nerve injury were found 15 of causalgia (Mayfield and Devin : SGO 80 631 1945) nd in none of these was the nerve lesion a complete division. Sympathectomy relieved 1 of them 1 was cured by fever therapy and 2 recovered spontaneously

Ganglionectomy combined with sympathectomy was successful in 7 pa tients of Freeman (Surg 22 68 1947) Only incomplete traumatic lesions of one or more nerves, caused by bomb or shell splinters, resulted in causalgia in the 48 patients of Barnes (JBoneJointSurg 35-B 172, 1953) who recom mended prompt sympathectomy

See Little (BMJ 1 1068, 1937) 6 cases; deTakáts (J 128: 699 1945) Evans (SGO 82 36, 1946) Rasmussen and Freedman (JNeurosurg 3 165 1946) 100 cases, Chinese soldiers Bingham (BMJ 1: 804 1947) 2 cases, trigeminal; Slessor (EdinMJ 55 562, 1948), 22 cases, some relieved by repeated procaine block; Sunderland and Kelly (AustralNZealJS 18 75, 1948) 278 cases of painful sequelae to peripheral nerve injury; Cullen (JBoneJoint Surg 30-B: 467, 1948) 24 cases Toumey (JBoneJointSurg 30-A 883, 1948) reflex sympathetic dystrophy; Mayfield (Causalgia, Thomas, 1951) monograph based on 105 military cases treated by sympathectomy

GLOSSY SKIN

Symptoms.—Much of our knowledge of glossy skin is the result of the work of Mitchell et al. (Gunshot Wounds and Other Injuries of the Nerves, Philadelphia 1864; Injuries of the Nerves and Their Consequences, 1872) The sites of predilection of the cutaneous changes are the extremities, particu larly the fingers. The affected skin is at first reddish or purplish, resembling chilblain. Later it becomes whitish or grayish in color, glossy and shining the surface somewhat resembling that of an atrophic, highly polished scar Fissuring and ulceration are likely to occur and atrophic changes are com monly present in the appendages of the affected part. In addition to the alopecia and the dryness or excessive moisture which is also sometimes present, the nails are generally involved and become curved both transversely and longitudinally There is usually more or less neuralgic pain. See Causalgia

Reflex Dystrophy of the extremities was reviewed by deTakáts (ASurg. 34. 939 1937) Vasomotor phenomena are prominent t first, but are later overshadowed by trophic symptoms. Hard, nonpitting edema is usually present. The edema is accompanied by paroxysmal pain, sensitivity to temperatur changes, and especial tenderness on pressure. The muscles are at first hypertonic, later becoming atonic. At first the skin temperature is raised; lat r it declines. The skin becomes glossy and bluish and is the site of eczem toid eruptions. Eventually there develop contractures nd shrinkage of the joi t cap les DeTakát interpreted the whole condition as a nutritional reflex, fixed self perpetuati g mecha ism. Of his 5 cases, 3 were helped by interference with the sympa thetic innervation.

A syndrome affecting the hand in 14 patients was described by Oppenheimer (SGO 67: 446 1938) manifested by swelling of the fingers, atrophy of the interossei narrow ing of the foramina of the homolateral cervical nerves and rarefaction of the bones of the diseased hand. Onset of symptoms took place overnight sometimes and was accompanied with pain like that f toothache The skin became thin and smooth, slightly glossy in some individuals; the nails were less shiny than normal, and the hairs were fewer No

changes of moisture, temperature or sensibility of pain occurred. The grip was weakened, and there was loss of fine prehension. Tingling and shocklike pains were experienced. Oppenheimer attributed the disorder to pressure on the nerves.

Etiology.—The disease is secondary to neuritis, and the neural lesion may follow gunshot wound disease of the cord, vascular disease (Fetterman and Spiller; J 114: 2276, 1940) or some constitutional disorder such as gout or rheumatism. All of deTakáts cases followed such lesions as might damage the blood supply to the sciatic nerve. Karnosh (JNervMentDis 84: 268, 1936) demonstrated 2 cases in which the evidence was clear that the cause of the change was damage of the vascular supply to the nerves. Causalgia is, with few exceptions, he pointed out, the peculiar property of the median nerve, the tibial portion of the sciatic nerve, and to a lesser extent the ulnar nerve. These are the nerves which anatomically are particularly vulnerable to vascular disturbances. The syndrome regularly follows infectious wounds or vascular diseases which produce occlusion and thereby cause nerve ischemia. Cervical ribs may cause trophic changes (Rubin and Cipollaro ADS 39 430 1939)

Prognosis and Treatment.—According to Mitchell, the condition ultimately runs its course, but the outlook is not good and pain is difficult to allay Tonics particularly vitamin B arsenic and iron may be indicated. The limb should be kept warm and precautions taken to guard against sudden changes of temperature For the relief of the pain the constant application of either cold or hot water should be tried. Some cases may be helped by sympathectomy Psychotherapy is certainly indicated at times, for Palmer showed me in 1944 that atrophy of an extremity can in large measure be the result of hysteria. The results of ACTH stellate ganglion block and other efforts were compared by Steinbrocker et al (J 153 788 1953) who obtained spectacular successes and unaccountable failures with each of the methods tried in the treatment of the shoulder hand syndrome

ERYTHROMELALGIA (ERYTHERMALGIA)

Erythromelalgia is a disorder of the extremities characterized by shooting throbbing or burning neuralgic pains, accompanied by congestion and patchy redness of the affected parts. This rare affection was described independently by Mitchell (PhilaMTimes 3 81 113, 1872 AmJMedSci 76 17 1878) and by Graves (Clinical Lectures Dublin 1864 p 826) The victims are usually males but the patient may be a woman rarely a child, for symptoms usually become manifest in middle age or later The affection may be unilateral or bilateral and 1 or both hands and feet or all 4 extremities may be attacked. There may be associated atrophic changes in the involved parts.

Characteristic features include (1) attacks of burning pain symmetric in the hands or feet (2) aggravation by dependent posture exertion or heat (3) relief by elevation or cold (4) flushing congestion and warmth of the skin during the attack and 5) refractoriness to treatment (Brown AmJMedSci 183 468, 1932) Exacerbations sometimes last for hours again for only a few minutes. Brown found augmented arterial pulsation demonstrable, along with a rise in temperature of the part when 33 to 34 C. is reached, pain always present The existence of a critical temperature above which symptoms arise and below which they fade away was confirmed by Smith and Allen (AmHeartJ 16 175, 1938) who preferred the name Erythermalgia (see PSMMC 14: 326, 1939) They distinguished the burning paresthesia of the occlusive vascular patient by the lack in such cases of temperature elevation of the affected extremities.

There are intense pain, usually of burning neuralgic character and some local elevation of temperature. Occasionally the attacks are apparently precipitated by slight pressure or friction and almost invariably the severity of the pain is aggravated by warmth and by gravity Sutton, Sr saw a patient whose disorder involved the palms, who would sometimes keep his hands elevated for half an hour or longer in order to alleviate his suffering. He stated that even the pressure of turning a doorknob would bring on an attack which might persist 10 or 12 hours The flexural creases of the hands became purplish or mottled during exacerbation and swollen so as to resemble cushions

Etiology.—Mitchell and Spiller (AmJMedSci 117 1 1899) believed the condition may result from either peripheral neuritis or changes in the nerve trunk at some point between the cord and the periphery Of 10 cases reported by Collier (Lancet 1 401 1898) there were evidences of multiple sclerosis in 6, tabes in 2, traumatic neurosis in 1 and myelitis in 1. Allen and Norman (USNMBull 35 309 1937) divided the cases into

those which are primary and those which are secondary to peripheral neuritis, polycythemia o thallium poisoning No evidence of occlusive arterial disease is found in the idiopathic type. Mufson (AmHeartJ 13: 483, 1937) found by capillaroscopy dilation of the subpapillary venule plexus with high hypertension in the minute vessels, the pressure there becoming high as soon s the skin temperature approached that of the blood. He thought the pain due to the hypertension in the small vessel He felt that the vascular response to rise in temperature is a normal one exaggerated by a pathologic absence of ormal antagonistic vasoconstriction; he gave adrenalin, therefo e, and found that in cases in which the pain was greatest the temperature fell most quickly

Similarity with symptoms of glossy skin (q.v) suggests that the basi of the disorder may lie in nerve ischemia, w rmth leading to superficial vasodilation which diverts blood from the deep structures.

Prognosis and Treatment.—The outlook is dependent on the nature of the underlying factor In cases lacking cord involvement the prognosis is fairly good. Relief is obtained by elevating and cooling the extremities, for pain is elicited when the temperature is raised above a critical point.

Symptoms are allayed by the avoidance of anything which produces vasodilation of the extremities. Aspirin in 10-grain doses may give relief that lasts for days (Smith and Allen) Hyposensitization to warmth by immersion of the parts in water the temperature of which is increased progressively with consecutive treatments, may prove helpful but this approach cannot be depended upon. X ray therapy may help Sympathectomy was reported curative in 3 instances (Telford and Simmons BMJ 2 782, 1940) Small doses of epinephrine relieve pain (Mufson AmHeartJ 13 483 1937) and the abnormal vessels respond to this drug in an exaggerated way indicative of an absence of normal antagonism. The patient of Markel (ADS 38 73 1938) also had gout and was relieved by sympathectomy after an unsuccessful trial of foreign protein therapy Any organic affection of the nerves should receive appropriate treatment Galvanism, with the positive electrode placed over the root of the affected nerve and the negative sponge gently stroked backward from the periphery sometimes proves helpful. Cooling applications, such as menthol in alcoholic solution or an ointment, may alleviate the pain temporarily

TROPHIC LESIONS AND PERFORATING ULCER

Trophic Changes occur especially in tissues which have been deprived of pain and temperature sensibility (Karnosh and Scherb J 116 2144 1940) Persistent erythematous lesions sometimes follow section of the fifth nerve and are limited to its distribution. Destructive lesions of the brain stem produce trophic disorders. Sores around the nasal alae especially just inside the nostril sometimes on the cheek or forehead occasionally occur after gasserian injections (Harris Brain 63 209 1940) Similar ulcers have been noted in lethargic encephalitis (Rosenberg and Solovay ADS 39 825 1939) The individual with a sensory loss is likely to finger and pick at the area more or less unconsciously producing lesions which are basically artefacts but which are likely to be interpreted as trophic in origin.

Organic brain disease is sometimes associated with interesting and unexplained skin lesions. Bullous eruptions of the sacral and posterior thigh regions were reported in 4 cases by Robertson (BMJ 1 291 1953) Several examples of bullous eruptions and bilateral edema of the legs and feet followed leukotomy (Ziegler and Osgood ArchNeurol 53 262, 1945) and multiple septic sores were seen in 14 patients who died following leukotomy (McLardy JNeurol 13 106 1950)

See Kreetin (QuartJM 31 177, 1937) seborrhea in Parkinson disease; Greenbaum nd Alpers (ADS 30 837 1934) [illegible] ulcer postencephalitic; Rattner (ADS 31 36, 1935), chloasma, factitious dermatitis, seborrhea, moles following encephalitis Ziegler nd Osgood (ArchNeurol 53 262, 1945) bullae on heels fter lobotomy; Bloom (NYSJM 47: [illegible], 1947) ulcers of heel and buttock following meningitis myelitis; Hopkyns (BMJ 1 [illegible], 1948), ankle ulcer in lumbar disc Wiener (Skin Manifestations of Internal Disorders, Mosby 1948, p 606), [illegible] (Dermatologica 100 [illegible], 1950), nasal ulcer following neurotomy of fifth ganglion Olsen (JNervMentDis 118 412, 1953) vesicular lesions in comatose patients, usually burns or pressure blebs.

Perforating Ulcer is a type of chronic ulcer of the extremities, characterized by the development of a deep sinus at some pressure area in association with neural or vascular abnormality. The affection is an occasional complication of central nervous system syphilis, spina bifida, leprosy and occlusive peripheral vascular disease. The earliest lesion is a callus or a ruptured blister near the base of the first phalanx of the great toe or on the heel. Suppuration takes place and the center sloughs leaving a superficial circumscribed ulcer surrounded by a thick, horny collar. Tenderness is wanting. Sinus formation may proceed slowly or rapidly. The lesions are usually single but they may be multiple. The majority of the patients are males, usually between 30 and 50 years of age. Kulowski and Perlman (ASurg 32: 1, 1936) reported 33 cases, 24 of which were in males. The causes were tabes in 2, vascular disease in 8, diabetes in 6, frostbite in 6, spina bifida occulta in 5, trauma in 4, and, in 1 each, obesity, encephalitis, manifest spina bifida, traumatic myelitis and x-ray injury. The 6 cases reported by Hardy (FinskaLäkHandl, Oct. 1935 p. 39) were in males; he named poliomyelitis as a possible cause.

The course is slow but progressive, and even if improvement occurs it is commonly only temporary. The condition can be ameliorated by rest and elevation of the part, but the lesions generally recur when the patient begins to use the limb again. Aside from treatment of the parent disorder, the management is conservative and symptomatic; amputation is a last resort (Tocantins and Reimann, J 112: 2251, 1939). Antibiotic ointments such as tetracycline may be helpful.

SYRINGOMYELIA

Syringomyelia is a disease of the spinal cord manifested by sensory and trophic changes particularly in aeral tissues of the upper extremities. The patient, generally middle-aged, shows slowly developing sensory loss, followed by motor defection usually beginning in one upper extremity. Diagnosis is not stereotyped (Putnam, MedClinNoAm 19: 1571, 1936), but dissociated sensory loss in the arms, muscular atrophy of the hand, and painless burns are practically pathognomonic. Failure to experience pain results in the patient's unwittingly injuring himself, and the cutaneous lesions are blisters and ulcers, which are painless.

Occasionally paresthesia, analgesia or the development of one or more whitlows may be the earliest appreciable manifestation of the presence of the disorder. Morvan (GazHebddeMéd 20: 580, 590, 624, 721, 1883) described that form of syringomyelia which is characterized by painless ulceration of the finger tips and paralyses and atrophy of the forearms and hands. "Morvan's disease" is also known as "Analgesic panaris."

In addition to the cutaneous and muscular atrophy which ultimately results, hyperhidrosis, reflex disturbances, sensory changes, contractures and necrosis are not uncommon. The legs are occasionally attacked, as well as the arms. In one patient large bullae frequently developed on the backs of both hands. The distal phalanges are often overlong, and a relationship with arachnodactylia has been postulated (Barron: NCarolMJ 3: 353, 194_). Facial asymmetry, a thin face with chin sharp and nose off center, is usual. The malady may bear a striking resemblance to neural leprosy; other manifestations of which can be found if leprosy is present.

Syringobulbia is the name applied when the medulla is involved. Trophic ulcers of the face and neck resulting from this were described by Schwartz (ADS 41: 153, 1940).

Pathologic changes are found in the cord, and consist of cavities in the posterior horns. The cysts are thought to be degenerated gliomas representative of a mesodermal defect in dorsal closure of the embryonal neural tube.

The disease is incurable; the treatment simply palliative. Tonics and galvanism may be employed. The cutaneous lesions are to be treated symptomatically, care being taken to guard the affected parts from trauma and

extremes of temperature. Surgical attack, with laminectomy vertical cordotomy and drainage of the fluid from the cavities, has been undertaken with improvement in some cases (Kelley: BMJ 1 610, 1935) Pain, spinal block and disability are indications for surgery Half the patients reviewed by Frazier and Rowe (AnnSurg 103 481 1936) were able to return to work after vertical cordotomy in the midline or a few millimeters to the side in the levels of greatest cord damage. If drainage is not accomplished, a second operation may be indicated. Myelotomy resulted in arrest or improvement in 17 and failed to prevent further loss of spinal cord function in only 7 of 24 patients of Wetzel and Davis (ArchSurg 68 570 1954) Royle (J 110: 1264, 1938) stated that superior thoracic ganglionectomy causes increased drainage of spinal fluid in hydrocephalus and syringobulbia, and lumbar sympathectomy is effective in syringomyelia. Putnam (1936) preferred x ray treatment of the cord, early in the disease Deep x ray therapy was said to have helped 70% of the cases (Gurevitch et al. AmJRoentg 1937 p 416); if radiation is successful, pain sensation returns first, then thermal then motor function.



Fig. 1019.—Perforating ulcer in tabes dorsalis

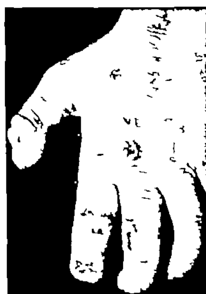


Fig. 1020.—Syringomyelia, with trophic lesions.

Arachnodactylia (Dolichostenomelia Spider Feet Marfan's Disease; Hyperchondroplasia).—The syndrome consists of abnormally long fingers and toes, hypoplasia of subcutaneous fat, underdevelopment of skeletal musculature, relaxation of ligaments, and, in half the cases, bilateral dislocation of the lenses of the eyes. Prominence of the ears, high-arched palate a tendency to infantilism, skeletal deformities of the thorax and vertebrae with kyphosis, scoliosis and asymmetry and deformity of the joints, especially of the feet, with contractures, are also features (Futcher and Southworth AIntM 61: 693, 1938)

This developmental disease appears to be due to malformation of mesodermal derivatives distinct from status dysraphicus (Piso et al.: AnnIntM 10: 1130, 1937) It is usually congenital and may be inherited as a dominant character. Of a family of 40 individuals, 17 had symptoms with considerable variability in the expression of the syndrome (Lutman and Neel AOphth 41 276 1949) Several showed the triad of arachnodactylia, dislocation of the lenses and cardiac abnormalities, while other members of the family were so mildly afflicted as to have gone unrecognized but for their genetic background. Cardiac malformation in relation to arachnodactylia, not rare was reviewed by Fischl and Ruthberg (J 146: 704 1951)

See Achard (BullSocMedHop 19: 834, 1902); Weve (ArchAugenh 104: 1, 1931) 32 cases reviewed, most of them younger than 10 years; oldest reached 61, 47 and 40 years of age. Passow (MünchMedWchr 81 1243, 1934) Adams and Porter (SouthMJ 42 844, 1949) Negro case.

PSYCHOSOMATIC ASPECTS OF DERMATOLOGY

The transition from conventional and old fashioned thinking about the nature of disease is in an active state of flux such that the word psychosomatic itself grates upon the sensibilities of many an expert in psychiatry competence in whose province I do not claim.

Materialism is wholly unsatisfactory as I have pointed out in lay lectures, utilizing such an elementary argument as this you can have a leg cut off and still be you, and another leg and a couple of arms, and ears, and the appendix removed and the tonsils yet all the while you have not *been touched as these things were being done to something that is yours.* So by extrapolation the body may be removed, yet the self persists. And the ego is a more significant reality than the body Mentation, intellectual emotional or subconscious, takes precedence over the most patently material objective man made thing for the very building in which you sit, made of bricks and cement and steel girders, existed in the desires and imagination of a mind and was drawn on paper before it was constructed. In considering an individual who is ill, one is rightly importuned to turn from the local manifestations to contemplation of the pathology of the person ' (Wright Clin 3 711 1944) *and in dermatology to* reflect upon the skin as an organ of expression.

The overlapping of dermatology and psychiatry received the consideration of Gotteaman and Menninger (ADS 59 367 1949) Some emotional disturbance often accompanies and follows some cutaneous disorders, but what cutaneous lesions owe their origins to disturbances in emotions is not decided. Disturbances of equilibrium of personality may combine with other factors to produce in some persons conditions for which they seek help from a dermatologist but might equally appropriately consult a psychiatrist

To be a *good doctor—dermatologist,* psychiatrist or of other especial interest—one must be sensitive and perceptive of the kind of person the patient is what he does, what he thinks and what he feels, and if possible, why Personology the study and treatment of men and women as persons, is the designation that fits this science (Sadler Practice of Psychiatry Mosby 1953) Sadler quoted Crookshank on the dilemma of the die-hard organicist I wonder that some orthodox physician does not describe emotional weeping as a new disease calling it paroxysmal lachrymation and suggesting treatment with belladonna (which dries up bodily secretions like saliva and tears) astringent local applications, avoidance of sexual excess, tea coffee tobacco and alcohol and a salt free diet with *restriction* of fluid intake proceeding in the event of failure to early removal of the tear glands

A physician blessed with insatiable concern for the human beings with whom he deals becomes a good amateur psychiatrist. He will listen with sympathy and advise with wisdom The ability to do these things characterizes the physician who is able to help his fellows with their emotional difficulties. It is educational indeed for the physician to have had some difficulties of his own, which let us hope he has surmounted, so that he may possess the insight that comes from experience. He can then do about as much for accessible patients as anyone can With patients who are *not* accessible one frankly does not do well nor do the psychiatrists I have met achieve much that is noteworthy as a rule Few of us who are mature have escaped episodes of anxiety so we know that it is harder to endure mental suffering than physical that it is easier to bear organic illness than chronic fear and that a day of physical labor is by no means so wearing as a quarrel with one s wife.

The capacity of emotions to evoke dysharmony of bodily functions is conspicuous their maleficent influence on the body as well as on the conduct *is obvious.* The rational mind is not capable of commanding the emotional

mood, but it can discount dysharmonies when they crop up and it can direct conduct so as to enable the person to make headway in trying to get out of his maze. It greatly helps a patient with superficial psychoneurotic problems to know that he is understood and that he is not uniquely different from others who are distressed. He can talk and think his way out of them if he is listened to attentively, sympathetically and with sincerity One may request an individual in a mild anxiety state to commit his problems to writing This of itself clarifies his thinking Sometimes he is then able to put his list in a drawer and forget it at least overnight. He can tackle his problems once they are defined one by one, and defeat them in detail, whereas when a dozen puzzles bedeviled him simultaneously he was only confused. This suggestion applies only of course to rational patients who are temporarily overloaded, but these are encountered frequently

Patients too deeply involved to respond to such an effort must be recog nized and guided into the supervisory care of psychiatrists. A dermatologist attempting to go beyond his capabilities in another field of medicine is as far wrong as if he were attempting to remove a gall bladder Given simply good sense, he will attack only the problems in which he is competent and avoid undertaking what he cannot do To place a patient in the hands of a psychi atrist is no small problem in itself (Wright: ADS 60 303 1949)

As the inflammatory reaction is featured by *dolor calor rubor* and *tumor* so the psychoneurotic reaction involves *dolor pallor sudor* and *tremor* The sufferer from emotional tension may experience stomach trouble and may at tribute his woes to this, as every practitioner knows and the sufferer from psychosomatic difficulties may manifest cool, sweaty extremities and pom pholyx which is prone to become secondarily infected and is almost incurable by materialistic medical means.

This approach embodies the thinking whereby dermatologists move grad ually toward views expressed by Stokes et al. (AmJMedSci 198 577 1939; 200 560 1940) Obermayer (J 122 862, 1943) and Becker and Obermayer (Modern Dermatology Lippincott, 1946) The last provide an essay under their discussion of neurodermatitis, on the mechanism and correction of functional dermatoses which must be read by those interested. In brief they ex plain to the patient his nervous irritability and exhaustion, of which he is more or less unaware until they point it out they endeavor to reassure to hold confidence to save the patient s face by attributing his nerves to his in heritance, and to teach him to relax by diminishing his ambition, by inducing him to take vacations, and by putting him prone daily under a sunlamp and in afternoon naps and they give him mild sedation with phenobarbital if this appears justifiable.

How much of their thesis with respect to neurodermatitis (q v) deserves acceptance it is not possible for me to say for through the peculiarities of my own make-up, I am skeptical. The benefits from cortisone vitamin B_1 and high protein diet in treating neurodermatitis suggest that organic disease is as much concerned with its causation as psychiatric difficulties are. I suspect that fatigue phenomena are concerned and that fatigue as an etiologic factor in some cases of dermatitis is itself the result of emotional causes. The mechanism whereby in medicine the mind affects the body remains obscure that it does so by way of intermediary biochemical mech anisms I do not doubt. See Etiology psyche (p 60)

A sensible statem at concerning the nature and influence of emotions as tiologic factors in disease was given by English (ADS 60: 1063, 1949) Basically important are the need for love and approval; anxiety fear and worry; hostility inferiority ambivalence guilt, ambition and competition, and envy Neurotic excoriation may be motivated by the objecti e of escape from being ignored. Itching may represe t a desire for love. The mechanisms of adjustment were interestingl defined by Menninger (JKansMS 44; 225, 1943), who listed compensation, sublimation, rationalization, symbolization, introspection, identification, condensation, idealization, repression, displacement phantasy ambivalence, projection, a d dissociation. The terms are technical ones. If one comprehends them, one may find cl es to the reasons for existence of dermatoses which have psychiatric relationships.

Undertaking to list dermatoses in groups according to the degree to which psychiatric etiology is significant, Sneddon (BMJ 1: 472, 1949) offered the following tabulation: (1) Those always psychic in origin: delusion of parasitosis, other obsessional states, dermatitis factitia, neurotic excoriation, trichotillomania; (2) Those with a large psychogenic factor: neurodermatitis, pruritus ani et vulvae, atopic eczema, nummular eczema, rosacea and (3) Those sometimes precipitated by psychogenic factors: urticaria, hyperhidrosis, pompholyx, seborrheic dermatitis, psoriasis, alopecia areata.

Literature on the relations of the psyche, soma and skin is voluminous and more or less illuminating. I quote an article by Cormia (ADS 53: 601, 1947): As the eye is the mirror of the soul, so may the skin reflect the psychosomatic personality and its struggles with life. Conflict and tension are produced, and they may be partially relieved by the development of somatic symptoms. These symptoms are an expression of and a defense against conflict. Weiss and English (Psychosomatic Medicine, Saunders, 1943) spoke of organ language by which a mute, repressed patient expresses himself. A patient with neurotic vomiting is trying to relieve himself of a personally nauseating or intolerable situation; one with hysterical blindness is shutting out unwelcome sights. The symbolism of symptoms is nowhere better shown than in the skin. It is expressed both in the type and in the localization of the dermatosis. The skin has the power of expressing many bodily emotions, including those of worry (picking), anxiety (pruritus and sweating), fear and anger (urticaria), guilt and shame (blushing and rosacea), hostility, masochism and eroticism (dermatitis factitia) and sexual pleasure (cutaneous masturbation). A patient with urticaria may be bursting the bonds of restraint; pruritus and excoriation may represent a martyrlike expression of a desire to scratch a disagreeable environment, while severe dyshidrosis may reveal an unconscious protest against using the hands for an irksome or fearful duty. Similarly a patient with rosacea is branded with the permanent guilty flush of self-consciousness and social anxiety. A victim of factitial dermatitis openly expresses his hate, social resentment and antisocial (destructive) tendencies and at the same time exhibits in obvious fashion his demands for attention and sympathy (narcissism or self love). A person also attempts, by the localization of his dermatosis, to point out the portion of his environment with which he is coming in conflict and at the same time to make even more clear the essential nature of the conflict. A patient with generalized pruritus is resentful against his entire environment; pruritus involving the genital region may be due to a sexual conflict, and pruritus ani may be symbolic of a latent homosexual tendency. Alopecia areata of the scalp is symbolic of a hole in the head and as such may express inadequacy. Case histories exemplifying such conceptions are given by Cormia, and are typical psychoanalytic reports in that they convey conviction to some and provoke in others a desire for an explanation more likely to be true.

Attention may be called to several individual psychologic studies. One by Wittkower and MacKenna (BJD 59: 281, 1947) indicated that subjects of seborrheic dermatitis are more likely to be grossly inhibited in social contacts, conscientious, worrisome, anxious and unable to relax than members of a control group. The authors aimed at unbiased expression, and the conclusions were adequately hedged. See also Acne, etiology. Rogerson (Pract 142: 17, 1939) related the history of a child of 10 years who, living at home in a difficult environment, was sensitive to fish and Brazil nuts. His sensitiveness took the form of an outbreak of urticaria when he came into contact with these substances. When he was away from home, happy and free from anxiety, he was able to eat fish of all kinds with impunity. The coexistence of allergy and psychosomatic symptoms was remarked upon by Karnosh (PsychiatQuart 18: 618, 1945).

No specificity of personality among patients with neurodermatitis could be detected by Obermayer (ADS 65: 291, 1952) by a meticulous psychiatric study of 13 patients. Utilizing psychiatric therapy, Cormia (BJD 63: 83, 129, 1951) achieved not one cure of a patient with a general or scattered pruritus, lichen Vidal, phobia or factitious dermatitis.

In many publications which describe psychosomatic mechanisms in skin diseases, there is an amazing ignorance or disregard of the known natural course and fluctuations and spontaneous remissions of the dermatologic manifestations and a common failure to eliminate post hoc propter hoc reasoning along with a lack of respect due the trap of the cart-horse fallacy, stated Sulzberger and Baer (YBD 1951, p. 30). The frustration and misery produced by the seemingly hopeless dermatoses of some unfortunates, interfering with peace, success and social and sexual adjustments, are amply adequate to cause psychic and emotional aberrations. There is great danger in attributing to preponderantly psychogenic causes dermatologic diseases which are in reality due primarily to other mechanisms. The physician may easily delude himself that whatever disease he cannot speedily diagnose and remedy by other means must be due to the mind and emotions (Sulzberger and

Zaidens abs YBD 1948 p 534) A psychological explanation in many dermatoses is regarded as the last resort of the diagnostically destitute by Loewenthal (SoAfrMJ Nov 17 1951) Yet the report of unilateral elimination of the deformity of ichthyosiform erythroderma by means of hypnosis appears creditable (Mason BJD 2 422, 1952 BMJ 1 220 1953)

Self inflicted lesions are conspicuously psychoneurotic in etiology while other lesions are sometimes psychologically explained in a manner borderline, dubious, or to me, incredible. Many an observer sees from within outward in his mind reading the distinction of fact from fancy being extremely tenuous. Time after time I cure pruritus by excluding contact irritants, correcting hypoproteinemia or eliminating overingestion of caffeine in a patient with a diagnosis of nervous imbalance. The psychiatric approach undeniably may accomplish respite from medication, much of which is irritating so that the skin heals, since it is let alone (Sutton DMoMA 44 481 1947) If feelings influence the thoughts of those who discuss these problems in these ways it is safe to say that the psychiatrically inclined are as intensely so influenced as those who profess to keep their feet on the ground and who in moments of levity compare some published psychoanalyses of patients with obscure dermatoses to the interpretations put upon cranial bumps by the phrenologists of old.

See Stokes et al (ADS 31 470, 1935) psychogenic dermatology; Klauder (ANeu of 33 221, 1936) influence of skin on psyche and psyche on skin Bernstein (JNervMentDis 87 1 1938), emotional factors in dermatoses Gillespie (BJD 50 1 1938), relation of skin and mind Hopkins (ADS 37 1035, 1938) psychologic itching Alvarez (MinnM 23 787 1940) "that tired feeling" Stokes and Beerman (PsychosomM 2 438, 1940) psychosomatic correlation of allergy bibliography Nelson (JPediat 19 632, 1941) pruritus and maladjustment in children Stryker (SouthMJ 35 192, 1942) functional dermatoses; Forman (BJD 59 45, 1947) narcosynthesis with Evipan Abramowitz (NYSJM 48 1037 1948) placebo therapy Schneider and Kesten (JID 10 205, 1948) psychogenic itching, cases Wright (SouthMJ 42 951 1949) management Shoryon et al. (BMJ 2 1300, 1950) abreactive technic in psychologic treatment of skin diseases.

NEUROTIC EXCORIATION AND DERMATITIS FACTITIA

Synonyms.—Feigned eruptions Dermatitis artefacta Pathomimesis Hysterical gangrene Autophytic dermatitis.

Self Inflicted Lesions were classed by Stokes and Garner (J 93 438 1929) as neurotic excoriation of the skin, probably including habit tics, hysteric dermatoses, and malingering with intent to deceive The term Pathomimia cutanea was derived from *pathos* disease, and *mimos* mimic.

Neurotic Excoriation.—Adamson (BJD 27 1 1915) reviewed the classes of self inflicted lesions of the skin in which deception is not an essential feature Such cases have been described under many names. Neurotic excoriation was interpreted by Zaidens (JNervMentDis 113 395 1951) as an effort to relieve tension, resulting in a specific type of compulsive behavior dating back to early fears and rage toward authority

These cases may be included within 4 types (1) neurotic excoriations or dug-out lesions (2) acne urticata (3) excoriated acne (q v); and (4) self inflicted lesions made without intent to malinger (auto-lesionism) Women are more often affected than men. The excoriations may occur on any part of the body but the face lateral aspects of the extremities and shoulder regions accessible to the finger tips are the sites of predilection. Lesions are produced by picking digging or scratching which may be quite unintentional and may constitute a more or less unconscious habit analogous to nail biting

It was emphasized by MacKee (ADS 1 256 1920) that the patient has no apparent reason for interfering with nature other than the nervous habit Emotional and nervous states in masochism and other sex complexes may lie in the background of neurogenous dermatitis. Psychiatrists sometimes go too far with the specious argument that, because scratching is pleasurable itching is a result of libido A sound personality may itch, scratch and be comforted,

but neurotic excoriation is rationalized by not induced by itching Excoriation often indicates sexual tension, sometimes immense boredom. Lichen spinulosus, responsive to massive doses of vitamin A (Garfield ADS 45 423,



Fig. 1021.—Neurotic excoriation in an old, lonely blind woman.





Fig. 1022—Sores and scars in an opium addict, from dirty injection (Dr Anstruther Davidson.)

Fig 1023—Injuries self inflicted by squeezing the ... t allay headache in ... Data ... ton path (Dr Hubert Ri... son)

1942) sometimes is responsible for the inconspicuous lesions that tempt the finger tips. Some of these patients need thyroid and improve when it is given (Goldblatt and Gordon JMed 21 480 1941) Extreme and interesting ex

amples were noted by Senear and Shellow (ADS 46 824, 1942) Psychiatric motivation was discussed by Michelson (ADS 51 245 1945) who stressed the necessity for studying the personality of the patient and recognized the dermatologist s incompetence in the specialty of psychotherapy

Figs. 1024 and 1025 —Neurotic excoriation of left side of abdomen by a right handed man and of right forearm by a left-handed woman.



Fig. 1026 —Trichotillomania.

Fig. 1027 —Lip sucking. (Dr Sam Sweitzer)

In the feeble-minded, bites are common self inflicted lesions (Butterworth and Wilson ADS 38 206, 1938) Biting sucking and similar oral preoccupations may produce circumscribed calluses resembling warts, keloids or even neoplasms (Ronchese: J 127: 1050 1945) The lesions seen in patients with multiple sclerosis by Byrnes (JNervMent Dis 82;

3 3, 1935) were attributed by him to trophic changes. In encephalitis, self-induced dermatitis was observed in 5 of 50 cases by Rattner (ADS 31: 35 1935) Chloasma on the forehead and seborrhea were also seen. The postencephalitic ulcer reported by Greenbaum and Alpers (ADS 30: 837 1934) was probably factitious.

Acne vulgaris, when asymmetric and localized, is often due to a postural habit, such as leaning on or fingering the chin, according to Stokes and Garner (1929), a keen observation therapeutically valuable. Erythema of the face was due to the habit of touching and stroking the face in agitation in the patient of Marshall (BMJ 1: 44, 1938) Irritation from the overuse of soap is common, affecting face or hands, and the acneic girl who tries to scrub away her lesions only injures the already sore skin.

In industrial dermatology one sees instances of prolongation of disease by persistent scratching, whether this be hysterical, unintentional or deliberate (Downing: AIndustHyg 1: 471 1930) Many a patient will continue to have dermatitis as long as it is advantageous to him, for example as long as compensation is being paid. This is true of morons as well as of "sharp" characters.



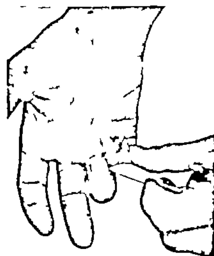


Fig. 1028.—Trichotillomania.

Fig. 1029.—Delusion of parasitism the patient demonstrates the method of removing "worms" from her fingers.

Trichotillomania is characterized by an abnormal desire of an apparently sane person to extract his own hairs. Children often do this, sometimes eat the hair they pull out. Raymond's designation *tic de l'épilation*, is an appropriate one. The scalp eyebrows and lashes are the parts most frequently attacked. Beinhauer (ADS 14: 59 1926) reported a typical example in an architect 48 years old. An extraordinary case in a morose boy of 7 was recorded by Sutton and Timme (AmJClinM 5: 402 1926) Three little boys under 3 years of age were reported by Bleyer (AmJDisChild 51: 336 1936) One youngster pulled out *the hair of his sister as well as his own* (Karrenberg DeutMWchr 61: 2006, 1935) Pseudo alopecia areata was the title used by Davis (BJD 4: 162, 1922) for this disorder An epidemic of such alopecia was observed in an asylum for girls by Semon (ADS 2: 785, 1923) One must distinguish alopecia areata and tinea capitis. The application of various antipruritics, such as phenol, menthol, camphor or tar, has no effect on the course of the disease. Guttapercha can be used as an impervious dressing. Trichotillomania is generally be cured by keeping the scalp shaved for several months. Efforts should be made to reduce the emotional tension of the affected youngster's environment, and parents require more treatment than the patient as a rule.

Trichoclasomania is like trichotillomania, but the patient picks at and breaks off the hairs instead of pulling them out (Sutton J 63 2126, 1914; 66: 185, 1916)

Onychotillomania.—The nail is damaged by picking (Alkiewicz: DWchr 93: 519 1931)

Dermatothelasia is a morbid state in which the person has an ungovernable desire to rub, scratch or irritate the skin of one or several parts of the body

Factitious Dermatitis is the title applied to injuries of the skin which are purposefully self inflicted usually to excite sympathy gain compensation, or escape duty. The lesions appear suddenly and range widely in character and

distribution. As a rule they are sharply defined, asymmetric and irregular in outline and are located on a part of the body readily accessible to the patient. Thus in persons who are right-handed, the eruption is on the left hand or arm the left side of the chest or the right thigh. Damage may be done by simple friction or by applications of lye acids, other caustic or irritating substances, hot metals or pointed instruments. Burns constitute about half of all cases of feigned eruption (Stokes and Garner 1929)



Fig. 1030.—Neurotic excoriation. (Dr George Miller MacKee.)



Fig. 1031.—Dermatitis factitia. (Dr Sam Sweitzer)



Fig. 1032.—Self-inflicted chemical injury limited to left arm of a right handed woman. Acid was applied with the stopper of the bottle.

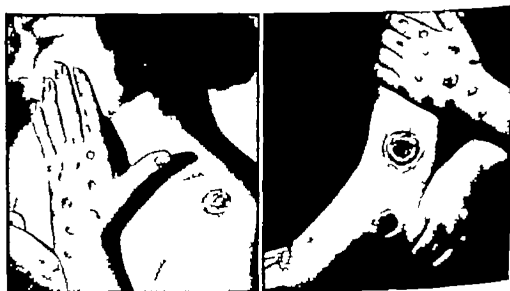
MacKee and Andrews (AmJRoentg 11: 617 1923) reported a case simulating x-ray dermatitis. The patient of Dotti and Veroni (RifMed 40: 775, 1924), a woman 40 years old, had for 7 years been inoculating herself with pus containing *Bacillus proteus* and more than 300 lesions developed during that time. Autoinjections of fecal material made the astonishing sores a woman exhibited to Sullivan and Torrow (SouthMJ 42: 402, 1949) All sorts of things were injected into herself by the patient of Laws (BMJ 2: 157 1951);



Fig. 1033.—Dermatitis artefacta. Phenol was the caustic used.



Fig. 1034.—Dermatitis factitia. A pai of sharp-pointed scissors was used (Dr H. C. Varney)



Figs. 1035 and 1036 —Factitious dermatitis circula keloids and gangrenous lesions.

pyrexia, cellulitis and lesions resembling erythema nodosum were so produced. In prisoners of war, Asel told me he saw bizarre lesions provoked by injections of cigarette lighter fluid. The patient of Grindon (JMoMA 26: 451, 1929) a middle-aged Jewess, complained that particles of crushed glass were "working out" through her skin; she misled her sympathetic relatives by secretly powdering herself with Epsom salts! The interesting patient of Brown (GuysHRpts 83: 356, 1933) was a girl 21 years old whose oral and perineal lesions were shown by psychoanalysis to be associated with masochistic auto-erotism. If a minute puncture wound is made in the oropharyngeal mucous membrane, one can hold the nose and mouth shut, expire vigorously and produce subcutaneous emphysema of astonishing appearance affecting the face and neck. This was done by prisoners of war observed by Reading (BMJ 1 103, 1930)

The peculiarities of the manifestations and the persistence of the eruption are valuable differential diagnostic points. The lesions are characterized by their want of similarity to a genuine disorder Straight edges abrupt angles and suggestive distribution are among the diagnostic features. Phobias and malingering are different problems (MacCormac BMJ 2 1153 1937) Care must be taken to exclude syphilis, tuberculosis, dermatitis herpetiformis, acne varioliformis lichen planus and chronic streptococcic ulcer Corneal and pharyngeal reflexes are regularly absent (Graham and Lewis: NYSJM 44: 621 1944) An ingenious artifice of authorship unknown to me, consists in telling the patient after one has become suspicious of him that his case of



Fig. 1037.—Factitious dermatitis. (Dr J Lamar Callaway)

extraordinary disease might be recognizable if it would only make its appearance in the usual locations, which one tells the patient are of course in places where he has not hitherto damaged his skin Following the suggestion given casually and with a straight face the patient sees to it that the disease does appear in the suggested distribution

In suspicious cases the patient should be secretly watched until positive evidence of guilt is secured then the patient should be told, privately firmly and quietly that the truth is known. Sometimes the use of fixed dressings, which prevent further injury to the part is helpful in diagnosis as well as curative Eaton and O'Leary (ADS 36 544, 1937) utilized the soporific state induced by giving Sodium Amytal during the effect of the drug it may be easier to obtain the patient s admission of guilt. This method was used with success in a patient of Saunders et al. (PSMMC 12: 65 1937) The plea for psychiatric management of these cases voiced by Bernstein (JNervMentDis 87: 1 1938) will hardly go unheeded. Psychiatrists are welcome to them but it takes a dermatologist to make the diagnosis. The hysterical or malingering patient does not desire psychologic insight so that psychotherapy is of limited value (Gandy SouthMJ 46: 551 1953)

See Cormia and Blight (CanadMAJ 33, 527 1935) case cured by occlusive dressing; Hartmann (DJD 48 542, 1930) 3 cases of excoriation and ulcers; Thomas (BMJ 1 864, 1937), gangrene; Lloyd (BMJ 1: 487 1938) associated with pregnancy Jaffrey (CanadMAJ 43 256, 1940) case; Levitt et al. (SoAfrMJ 14: 319 1940) caustic soda applied by narcotic

addict; Pillsbury (ADS 41 832, 1940) bizarre lesion dorsum of hand cured by occlusive dressing Freeman and Engeler (ADS 43 578, 1941) elephantiasic engorgement of legs from factitial constriction Klein (BullJHH 68: 469 1941), subcutaneous abscesses Benedek (JID 9 65, 1947) corrosives used on scalp; El Arina (JEgyptMA 31 889, 1948), trichotillomania MacCorma (BJD 60 106, 1948) linear excoriations in twins Dochas and Basqué (abs J 151: 773 1953) factitious abdominal ulcer into which woman put bits of cotton simulating maggots Lewis (ADS 63: 515, 1951) trichoclasomania Beck (Dermatologica 107 114 1953) 34 cases of self inflicted lesions.

Delusion of Parasitosis (Acarophobia)—The affected person believes and cannot be dissuaded from the conviction that he is infested with some parasite He will pick or rub off small particles of epithelial débris and insist that the masses are or contain offending organisms. The disorder may succeed upon an itchy organic disease or develop independently Innumerable negative examinations of the material make no impression whatever upon the patients, who remain firmly convinced that their integument is inhabited by a perhaps hitherto unknown species of small but exceedingly industrious creatures which will eventually prove their undoing The forcible removal of a few of the outermost corneous layers usually has a soothing effect on their minds, and after they have carefully destroyed the material and its supposedly dangerous contents they are at ease until a recrudescence occurs.

Acarophobia is found in persons with delusions of persecution and with family social occupational and sexual difficulties, most of them being women of middle age, single or divorced, essentially paranoid (Zaidens JNervMent Dis. 113 395 1951) Phantom dermatoses was the title by which MacCormac (BMJ 2 1153 1937) designated the imaginary dermatoses invisible to the examiner The patient may put onto the skin what he imagines to be there.

Phobia is misapplied in designating such conditions, according to Wilson and Miller (ADS 54: 30 1946) in their study of 51 cases, for the patient is deluded but not fearful. This is a symptom complex not sharply delineated from other delusions. It may occur in toxic psychosis, paranoid dementia praecox, involutional melancholia and paranoid states. The prognosis depends upon the variety of underlying mental error being more favorable in toxic and involutional psychoses and extremely poor in paranoia.

While the sufferer is usually psychotic, he may have only a severe psychoneurosis, stated Wilson (ADS 66: 577 1952) yet the disease indicates mental aberration beyond the scope of practitioners other than experienced specialists in psychiatry The delusion probably affords the patient a better mechanism for adjustment than any substitute a therapist could offer He should be treated tolerantly for to give him insight, if this could be done, would strip him of his only protective defense.

Before fixing the diagnosis one must be certain that infestation with the avian itch mite (q v) or comparable inconspicuous irritant is not at fault See also Filariasis and Paresthesia.

Treatment—I can occasionally keep the patient from damaging herself by arguing that external medication has done her no good, that the offensive agent may be attacked internally with a hope of success, and that injections may render the body uninhabitable the patient then receives an occasional shot of B complex or estrogen and is perhaps happier and better off Significant nutritional deficiencies were found in 4 patients by Aleshire (J 155 15 1954) the correction of which was highly beneficial. A method of treatment which gives considerable relief when the patient has not too many dug-out lesions is to inject each with a local anesthetic then destroy several cubic millimeters of dermis with the pointed actual cautery Whether this is psychotherapy or achieves the removal of an organic bit of neuropathologic tissue I cannot say I cling to the hope that an organic explanation of these cases may be discovered. An individual who was correct in believing he had an itchy crawling sensation would be no less difficult to persuade otherwise than an individual who was insane.

Other Delusions.—Klaude (J 85: 1683, 1925; ADS 37: 650 1938) reviewed the cutaneous neuroses exhaustively including bleeding stigmas, pruritus cured by psychotherapy (preferable in my opinion to irritant medicines) acarophobia and neurotic excoriations.

He described erythrophobia, the fear of blushing; syphilophobia (see Cormia: CanadMAJ 39: 361 1938); rupophobia, fear of dirt, commonly resulting in traumatic and chemical dermatiti ; peladophobia, fear of bald ess; bromhidrosiphobia, fear of being offensively malodorous topalgia, local pain of psychopathologic nature; and cancerophobia, fear of cancer

PRURITUS

Pruritus is defined as the symptom, itching Many dermatoses are itchy and itching symptomatic of diseases described elsewhere in this book receives mere mention. Idiopathic pruritus is defined as itching due to causes of which the diagnostician is ignorant. Pruritus as here used refers to states in which this symptom is the main one, provocative of excoriations and other lesions, but not caused by them. The primary symptoms are itching burning tingling and formication. Secondary manifestations, such as hyperemia, laceration, infiltration lichenification, pigmentation, secondary infection and lymphadenitis, develop as a result of scratching and parasitic complication.

Itching may be constant or intermittent. The disorder may involve one or several regions, or even the entire skin. Exposure to heat or cold in persons with temperature sensitiveness will excite an attack. In the type known as bath pruritus, burning and itching come on immediately after bathing and are usually due to contactants, the irritation of which is exacerbated by warmth soap is itself often the cause. Predisposing to bath pruritus is a dry thin skin, such as often accompanies auburn hair and freckles. Deficiency of thyroid or estrogen likewise can produce xerosis and a skin more than normally vulnerable to irritation. See also neurotic excoriation.

Domestic cooking may incite pruritus in heat-sensitive housewives, although allergy to kitchen fumes from fuel or food, or even a deep distaste for that kind of work, may underlie such attacks. The desire to scratch is almost irresistible and the objectively otherwise normal skin soon presents rough and even bleeding areas.

Generalized Pruritus.—The entire surface is seldom attacked at one time but the sensations develop at first one point and then another skipping about disconcertingly without appreciable cause. The common generalized variety is that occurring in persons of advanced age, pruritus senilis. This may respond to testosterone by mouth (Dobes et al. JClinEndocr 5 412 1945) It is perhaps a result of ischemic and atrophic changes in the skin. Hypoproteinemia is, I think a common cause of generalized pruritus (see Lichen simplex)

Anal and Genital Pruritus.—These are the parts most frequently affected in localized pruritus. While the disorder is usually attributable to mycotic infection trichomonad infestation, dermatitis venenata from medicinal or other contactants, varicose veins bacterial dermatitis, lichen simplex, kraurosis or other identifiable local, pathologic conditions, it is sometimes extremely difficult to locate the cause.

Pruritus Scroti is usually confined to the scrotum proper although the shaft of the penis and the perineum are occasionally involved. Lichen chronicus (q v) may develop with thickening redness and oozing Dermatomycosis and dermatitis venenata are the usual causes. Match box clothing soap or medicinal dermatitis is the sort of thing to suspect.

Pruritus Ani is an exceedingly distressing ailment. The anal, perianal or intra anal regions may be involved. Fissures and hemorrhoids are frequently although by no means invariably present. Irritation, thickening and induration, maceration, and even carcinoma may develop secondarily Contactant irritation is the usual main factor but fecal material is not I think. Pinworms may cause it, and leakage of mineral oil is often a factor Mycotic infection of the crotch (and feet) is commonly the cause in pruritus of the pudendal and perineal regions in members of either sex. Pediculosis, staphylococcic folliculitis, and toilet seat chemicals such as Lysol and chlorine are possible causes. Diabetic urine promotes bacterial growth, and niacin helps in pruritus of diabetic origin (Rudy and Hoffmann: NEngJM 227 893 1942)

Psoriasiform seborrheic dermatitis, lichen sclerosus and lichen chronicus simplex are stubborn itchy dermatoses of this region. Comedones in the anal region provoked pruritus in a case of Allington (ADS 59 490 1949) Coccic folliculitis and acne pustules are itchy in this location Seborrheic dermatitis may affect perianal hairy skin and produce pruritus (Foster and Hill ADS 41 699 1940) I have occasionally cured the anal complaint by concentrating efforts on the scalp see Seborrheic dermatitis. Pruritus ani following the administration of antibiotics has not been uncommon, for Aureomycin and Terramycin especially cause diarrhea, alteration of intestinal flora, and dermatitis sometimes intense, of the mucosal orifices (Kallet and Davolin J 149 1599 1952) see Moniliasis etiology (p 549)

PRURITUS VULVAE is common in pregnant women. Pressure and venous congestion are supplementary causes, and mycotic vulvovaginitis is common. Nail lacquer soap and perfumed powder are contactant possibilities. The gynecologist s point of view was presented by Jeffcoate (BMJ 2 1196 1949) who reported on 254 cases affecting nonpregnant women. The causes included trichomonas infestation, cervicitis cervical erosion, deficiency states, psychogenic causes, skin diseases not specific to the vulva, prolapse, leukoplakia, diabetes mellitus, fungus infection, senile vaginitis, contact dermatitides allergic states menopausal atrophic states and, finally in about 10% of the cases, unknown In the study of the patient history thorough and competent examination and appropriate laboratory work are required. I standardly determine the vaginal pH examine the hanging drop for trichomonas and make direct and cultural examinations for monilia. The red cell count hemoglobin blood sugar and often the serum proteins are determined. Gastric acidity may be measured to the advantage of a few patients. The history as it appertains especially to nutrition, chronic fatigue and emotional problems may be revealing

Pruritus Hiemalis and **Pruritus Aestivalis** are peculiar recurrent types which develop with the advent of winter and summer respectively Pruritus hiemalis is more common. The attacks occur as a rule at night when the patient is disrobing or in the morning when he arises. The paroxysm of itching lasts for an hour or more It finally dies down as the normal temperature of the skin is regained.

'Itchy Skin is th itching incited by light tactile stimulation of the area surrounding a localized injury o njection of histamine (Bickford ClinSci 3: 377 1938) The area is sharply defined and appears to be associated with the local axonic pathway the nerves i volved be ng not of the sympathetic system and separate from fibers responsible f r hyperalgesia and flare. This sensory response can be abolished by asphyxia or by cooling, wh ch do not influence the central itch sensation, so that a different nervous pathway must be postulated. An antipruritic state can be brought about, by faradic stimulation or by heat of 49 C. applied for 3 minutes, such that pricking the skin with histamine does not incite itching. The stimuli productive of the antipruritic state are pa ful. Tetraethylammonium chloride inhibits Bickford s itchy skin phe omenon, ccording to Sonnesheim t al (JID 1.1 321 1949) although it does not affect spontaneous itch, flare or hyperalgesia, pparently acting selectively on the axone system responsible for itchy skin.

Etiology—Tangible factors are changes in the skin such as occur in old age, jaundice hyperthyroidism, glycosuria, oxaluria, gestation, intestinal parasitism, lymphoblastoma and intolerance of drugs (see dermatitis medicamentosa) Hypoproteinemia and macrocytic anemia occurring in conjunction with chronic lichenoid dermatitis appertain to pruritus in some patients (see Lichen simplex) Achlorhydria is occasionally pertinent to a case of pruritus vulvae (Swift JObGyn 43 1053 1936) Urinary sugar was absent but the carbohydrate tolerance curves were abnormal in 3 patients with generalized pruritus reported by Zoll (ADS 61 491 1950) and correction of their metabolic error was followed by relief of itching Polycythemia vera is a rare cause of generalized, sometimes severe itching (Brumpt PresseM 60 1397 1952) it is easy to overlook.

Jaundice causes pruritus. In general, the deeper the jaundice, the worse the itching. Prelct ric pruritus occurred in 46% of the infectious hepatitis cases of Hoagland and Shank (J 130: 615, 1946) When the primary complaint of a jaundiced patient is itching there is usually present an obstruction of the extrahepatic passages, stated Thorek (J 142: 670 1950) who believed that patients with intrahepatic jaundice rarely complain of itch i g. Pruritu may occur in ja dice of any sort includi g those with hepatocellular l ver damage according to Brick (J 14. 198, 1950) The administration of thyroid diminishes the output of bile salts and so may benefit itching from jaundice according to Langdon-Brown (BMJ 1: 301, 1937) Ergot has a palliative effect too, but is transitory and if abnormal retention of bile salts is the cause of pruritus intermittent external biliary drainage can be used to obtain relief in cases of chronic hepatic disease such as hepatitis or cirrhosis (Varco: Surg 21: 43, 1947) The jaundice of acute hepatic disease is, however self limited. Androgen by sublingual absorption i a dose of 25 mg daily relieved itching fairly promptly in several patients with chronic obstructive jaundice so treated by Lloyd Thomas and Sherlock (BMJ 2: 1-39 193") producing a fall of serum cholesterol but it caused masculinization of 3 of the 6 females.

In localized pruritus, a causative factor can usually be unearthed. Local causes include fungi, roundworms, constipation, stasis due to gestation, hemorrhoids, fissures (streptococci?) kraurosis, dermatitis from medication (a common and important factor) dermatitis venenata of other sources, and lesions of lichen planus and other pruritic dermatoses. Itching due to fungus or trichomonad should readily be recognizable as such. Inconspicuous mycotic vaginitis may maintain an almost ineradicable monilial intertrigo with attendant pruritus. Inconspicuous interdigital or nail infection with *Trichophyton Epidermophyton* or *Monilia* may keep reinfecting the pudendal skin. Allergy in any of its forms may provoke itching Gases or dusts may act by respiratory absorption Soap clothing (wool silk, fabric finishes) cosmetics (including scented talcum and nail lacquer) and medicinal agents are to be suspected (see dermatitis venenata) Olive oil can cause pruritus. Pressure and posture may be concerned in some cases. In cardiac decompensation, the skin of the back, where the patient rests on it is likely to itch simply from inadequate oxygenation the same cause underlies the itching produced by a girdle.

In patients in whom attacks of itching are provoked by heat, effort and emotion, there are those who respond with urticaria and those who suffer generalized pruritus without urticaria. The urticarial group differ from patients with other varieties of urticaria in that attacks can be provoked by injections of derivatives of acetylcholine (Grant et al. ClinSci 2 253 1936) Nomland (ADS 50 247 1944) described patients of the type who itch when influenced by warmth but are not urticarial, and he observed the experimental precipitation of attacks by injecting intramuscularly into them 12 mg of Mecholyl chloride Attacks would start within 1 to 10 minutes and could be relieved by dousing the patient with cold water Cool, moist applications are generally palliative in pruritus, whatever its cause

Reviewing the physiology of the sensibilities, especially itching, Bishop (JID 11 143, 1948) noted that itch can be induced by the summated effect of weak electric shocks individually below the threshold of pricking sensation; itching, he believed, results from a particular pattern of stimulation of pain endings. The nerve track of the itch-scratch reflex lat rested Koenigstein (ADS 57 828 1948) whose experiment ndicated the ex istence of a scratch cente in the lower part of the medulla oblongata. While ergot or yohimbine prevented or suppressed the itch-scratch reflex ind ced in various ways, they did not influence it when it was induced by irritating intracisternal injections. In itchy human beings, injection subcutaneously of 1 mg. of dihydroergotamine may relieve itching (capable of doing harm; see dermatitis medicamentosa)

Treatment.—If possible, the cause should be located and disposed of. Generally speaking the diet should be simple and nutritious. Alcohol and coffee are likely to prove harmful. Alkalinization is worthless. Internal remedies often alleviate the discomfort, but bromides are prone to intoxicate. Aspirin is more suitable and is almost always harmless. Nervous patients with flabby dry skins often need thyroid extract, estrogen or vitamin A. The vicious cycle of insomnia, sedative coffee to excess, more pruritus, insomnia, sedative and coffee is commonplace It eventuates in exhaustion and drug

intoxication. Banks (J 100 328 1933) recommended subcutaneous injections of histamine, in doses of 0.5 mg twice daily in pruritus and urticaria. Foreign protein shock often proves helpful Small doses of potassium iodide give relief in some cases of senile atrophy with itching Papaverine hydrochloride 1 grain given intravenously abolishes itching for several hours (Bamber Pract 171 378 1953)

The antihistamine drugs given internally are often quite successful in palliating generalized pruritus. Antihistamine preparations for local application are little to be trusted for they frequently irritate or sensitize (Sulzberger and Baer YBD 1951 p 22 see Treatment antihistamines) These topical antipruritics are prescribed blindly for many a patient whose dermatitis might well be correctly interpreted and effectively treated with other medication if the physician were more painstaking or expert. They are worse than useless in impetigo infectious eczematoid dermatitis and poison ivy where their ill effects have come under my observation. Thephorin ointment was studied for example but not recommended by Baldridge (ADS 63 260 1951) Perazil cream seems to me superior to the others, and I occasionally prescribe its use on a small, dry pruritic lesion for which I have designed more definitive therapy but desire immediate palliation.

The topical anesthetic agents are rarely prescribed by dermatologists. Nupercaine ointment popular with proctologists is a frequent cause of contact eczema and a dermatologist uses medicines of this sort only when he is pretty desperate which admittedly he may become Ethyl aminobenzoate 25% in an ointment vehicle is commended with reservations. See Antipruritics (p 75)

External treatment is of great importance in all types of pruritus. The underclothing must be soft and nonirritating Old cotton and linen are preferable In laundering all soap should be rinsed out. Frequent bathing particularly in hot soapy water is to be avoided. Bran, starch, and oatmeal baths are sometimes helpful in generalized pruritus, particularly if the skin is carefully dried afterward by patting and a bland dusting powder applied. Recourse may be had to phenolated calamine lotion

R	Phenol	1.0
	Zinc oxide	
	Starch,	
	Calamine of each	90.0
	Glycerin	10.0
	Water to	180.0
Sig	Shake and apply *freely* to allay itching	

One must be alert to the possibility of intolerance of even simple and generally innocuous agents especially menthol, and even petrolatum or other bland ointment bases. Calamine is unsuited for long usage by the xerotic individual. Petrolatum or mineral oil is preferable to cold cream or olive oil. The following prescriptions for topical antipruritics may be useful

R	Camphor powdered	-.0
	Zinc oxide,	
	Cornst rch	
	Zinc stearate of each, to make	60.0
Sig	Dusting pow ler for relief f itching	

R	Phenol	0.3
	Salicylic acid	0.3 0.6
	Zi c oxide	
	Cornstarch	4.0-8.0
	Petrolatum to	30.0
Sig	Bland paste for relief of itching Cool compresses may be superimposed.	

R	Ethyl aminobenzoate	5.0
	Lanolin	4.0
	Petrolatum to	30.0
Sig :	Apply sparingly to stop local itching	

℞ Phenol 4.0
Potassium hydroxide 5% 4.0
Linseed oil .... to 50.0
Sig: Bronson's alkaline antipruritic oil to remove scales from localized lichenoid lesions.

A lotion followed by a powder was frequently prescribed by Bellario (1948) he told me phenol 1 glycerol 10 water to 100 then menthol 1 boric acid 5 talc to 100

Ointments containing 2% coal tar 2% ammoniated mercury or even 10 to 20% calomel, occasionally are of service in parasitic pruritus. A 10% camphor-chloral hydrate ointment is helpful in some instances. Applications of folded cloths wrung out in either cold or hot water often relieve. Cleansing should be accomplished by water alone without any detergent.

A grain of papaverine hydrochlorid may be given slowly intravenously yielding 1 to 6 hours of respite (Wirth: JID 8: 63, 194) Lipstein (ADS 53: 231 1946; 56: 373, 1947; 58 47 1948), acknowledging the hazards, used aminophyllin 0.5 Gm. in 20 cc. water intravenously for similar purposes. He obtained immediate relief of itching in some 80% of 30 patients, and their relief persisted for 11 hours, on the average.

For relief of intolerable itching, MacCormac (BMJ 2: 48, 1946) described temporary abolition of the urge to scratch by sedation with intravenous Novocain 0.1% 1,000 cc. given in a hour period daily or by continuous narcosis with Somnifaine. Beinhauer (ADS 57: 1019 1948, see ADS 65: 39, 1952) described the use of tribromethanol (Avertin) 60 to 100 mg. per kg. f 6 or more days in the alleviation of desperate pruritus i various conditions. Ethyl alcohol, 5% in isotonic saline, may be used intravenously in doses of 500 to 1,000 cc. of the dilution, with little hazard and good temporary narcosis.

In anal and vulvar pruritus, a cause can generally be found, and purposeful treatment rather than symptomatic can be chosen.

Treatment by tattooing with cinnabar is an interesting enterprise, which helps some patients. Hollander (ADS 38: 837 1938) cured all of the 15 cases he reported a d said, in discussi g paper by S lzberger (ADS 40 493, 1939) that he had, by that time, cured 40. Turrell and various collaborators have written at length on this subject (AmJObGyn 40: 834, 1940, JID 3 289, 1940 ADS 41: 5*1, 1940; AmJObGyn 4 200, 1941; AnnSurg 115 1*6, 1942; Surg 23: 63 1948) observi g occasional failures and a few instances in which mercury incited eczema. Were I the patient, this approach would be close to the bottom of the pile of possibilities.

Employment of anesthetizing substances by injection the sectioning of nerves and undercutting operations are rarely prescribed by dermatologists, but surgeons, being less resourceful with topical efforts, frequently resort to such methods (Steinberg NEngJM 215 1019 1936 Swinton: SurgClin NoAm 19 689 1939) The scrupulous hygiene recommended by proctologists often results in soap dermatitis. Dietary restrictions, popular with proctologists seem rarely consequential to me In fact, proctologists average being as incompetent to treat mucocutaneous disease distal to the rectum as dermatologists are to treat carcinoma of the sigmoid.

Estrogen may benefit the patient with kraurosis (q v) or menopausal changes (Hawkinson: J 111 390 1938) Estrogen in overdosage aggravates pruritus which may then be relieved by wheat germ oil, according to Shute (*J 110 889 1938*) The topical application of estrogen may yield better results than its systemic administration (Kevorkian NEngJM 220: 661 1939) While stilbestrol suppositories are in common use by gynecologists, I have not had much success with them. In addition to diethylstilbestrol, good diet, thyroid extract and vinegar douches were recommended in managing senile vulvovaginitis by Ararbanol et al (J 121 1123 1943) Estrogen ointment and parenteral estrogenic substances greatly benefited the majority of 54 cases reported by Klaften (JClinEndocrin 3 218 1943)

Cortisone and ACTH (Fromer and Cormia JID 18: 1, 1952) have their place in therapy being palliative and greatly relieving especially in cases of the lichenoid eczema type Hydrocortisone acetate ointment helped 26 of 29 patients of Alexander and Manheim (JID 21 223 1953) and some of Turell (*J 158 173 1955*) depending on the cause.

Phenobarbital, ¼ grain q.i.d., is wonderfully beneficial, occasionally

A powder often helpful in anal itching consists of equal parts of bismuth subnitrate and zinc stearate

All cases of pruritus demand investigation of etiologic factors, which can generally be found. Treatment cannot be standardized. Pruritus is as bad a diagnosis as eczema Korth told me that proctoscopic examination in pruritus ani often reveals rectal inflammatory puncta, and that in such cases the instillation of Mercurochrome solution a dram to the ounce of water is beneficial. X ray therapy should be used only in the treatment of a specific disease and undiagnosed itching of anal or genital regions is not of itself an indication for roentgenotherapy When one knows what dermatosis is present and knows *further that x ray therapy is useful in that condition, then* the correct use of the modality is appropriate

The safest and most effective single topical application for relief of itching is cold water which may be used in the form of a cool shower a tepid bath a wet towel laid upon or wrapped around the itching parts, or a block of ice Sometimes brief exposure to extremely hot water provoking initially a veritable ecstasy of itching is followed by welcome though temporary relief.

To cure pruritus the cause has to be eliminated. It is fortunate that the action of many a cause is self limited. When this is not so the patient and the doctor may have their troubles.

PRURITUS, ETIOLOGY AND TREATMENT Dunhill (BMJ 2 1034 1934) in Graves' disease Klauder (PaMJ 37 720 1934), pathogenesis Prinzmetal (ADS 30: 842, 1934) nitrites relieve some generalized cases Horder (Lancet 2 237 1935); Fantus and Cornbleet (J 106 2144, 1936) therapy Lichtman (J 107 142, 1936) ergotamine Genner (ActaD-V 18 244, 1937) bathing can be overdone Haldin-Davis (Pract 141 741, 1938) winter dermatoses Stillians (J 114 1637, 1940) treatment Nomland (JIowaMS 30 468, 1940), generalized Anderson (NEngJM 227, 651, 1942) senile Feldman et al. (ADS 46, 112, 1942), hormonal deficiency Wien (IllMJ 81 125, 1942), etiology, Arnold (BJD 61: 60 1949) winter pruritus, Carter and Eusman (J 142 277 1950) danger to heart of intra enous procaine; QMN (J 142 1397, 1950) dangers of procaine, Rottino (PSExperBiol 71 379, 1949) adenylic acid (my B-den) which was found ineffectual by Sawicky et l. (JID 17 244, 1951) and by Pearson and Fromer (ADS 64 302, 1951); Epstein et al. (Allergic Pruritus—Its Dermatologic Management, Bruce Publ. Co., St. Paul, 1952), Caiman and O'Neill (BJD 64 274 1952) itching in tension states Cornbleet (JID 20 105, 1953) length of scratch in pruritus inversely related to density of tactile organs Forman (BMJ 1 306, 1954) range of etiologic possibilities and the pleasure of scratching; Edwards (BMJ 2 1527, 1954), melancholia, with pruritus, 6 cases helped by electric shock therapy; Davis and Moorsand (AD 71 224, 1955) static electric charges deleterious in xerosis Hicks and Mullins (AD 71 46, 1955) mottled brownish discoloration of the face and pruritus sim lating neurodermatitis in xanthomatous biliary cirrhosis, the liver disease without jaundice oftenest causing pruritus of hepatic origin.

PRURITUS ANI ET VULVAE Castellani (BMJ 2: 1037; 1040 1928) mycotic anal itching Wilson (NoWMed 33 263 1934) alcohol injection; Netherton (MedClinNoAm 19 1191, 1935–36) phenolphthalein cathartive; Epstein and Sexton (UCalRev 41 864, 1937), inflammation of Cowper' gland, prostatitis, seminal vesiculitis causing anal itch; Bacon (AmJDigDis 4 109, 1937) injection of distilled water Hollander (ADS 36 141, 1937) trichomonas, Vayssière (GynecOb 36: 209 1937) 100 vul ar cases, etiology and treatment Usher and Campbell (CanadMAJ 38 432, 1938) kin changes after nerve section, Castellani (JTropM 41 377 1938) mycotic Terrell and Terrell (SouthMJ 31 907, 1938) majority mycotic Spiesman (AmJSurg 42 356, 1938) pectenotomy Manheim and Brockerman (SGO 67 800 1938) excision f anus Manheim nd Marks (AmJSurg 39 66, 1938) eucupine-procaine injection Usher and Campbell (CanadMAJ 38 431, 1938) erve sectioning; Wilson (J 110 492, 1938) alcohol injection Dracoulides (RevfrançD 46 735, 1939) Lamblia intest nal as cause Dabney (SouthSurg 8 232, 1939) nicotinic acid for pruritus vulvae; 104 Burnam (MedClinN Am 23 309 1939) vulvar Hailey and Hailey (ADS 40: 726 1939) diabetes cases, 80% with eczema elsewhere, Wiener and Strakosch (J Lancet 60: 532, 1940) diabetes Granet (NEngJM 223 1015, 1940) syringe rectum Speare and Mabry (NEngJM 223 274 1940) 175 nal cases, individualize treatment Wharton (SouthMJ 34 694, 1941) vulvar; Swinton (NEngJM 236 169 1947), therapy f anal, Driver et l. (ADS 59 242, 1949) coparaffinate ointment Hailey (J 139 837, 1949) 520 cases Lynch (J 150 14 1952) 113 cases, review Macalpine (MacKenna Modern Trends in Dermatology Butterworth & Co, 1954) reactivation of infantile unconscious fantasies centering on procreation within bdomen Vogt (MoMed 51 187 1954), causes of pruritus vulvae discernible and curable by direct attack as a rule Baumeister (J Lancet 74 89 1954) cortisone topically and orally often helps

COWHAGE PROTEIN IN PRURITUS.—The hort, barbed spicules covering the seed pods of the tropical plant, *Mucuna pruriens* re exquisit ly effectual as a stimulus for itching Shelley and Arthur (AD 72 399 1955) found it possible to incit itching without ny linical sign by inserting int the skin a singl cowhage spicule. From cowhage they isolated purified and identified a plant proteolytic enzyme mucunain. They postulated that activation or release of serum proteinases in the epidermis may be the basis fo clinical pruritus, for proteinases are uniquely pruritogenic The pruritogenic principle of cowhage could not be histamine, for it did not incite wheals. See Foreign Letter England (J 150 63, 1953) also Trichome dermatitis, p. 94.

DERMATOSES OF UNDETERMINED CAUSE

It may be said that the dermatologist in the course of much of his work does not know exactly what he is doing or why he is doing it. This is not because investigative work has been either dilatory or unremunerative nor does the fact connote an attitude of defeatism regarding the ultimate solution of the myriads of problems facing us. The challenge is one to fill the inquisitive spirit with enthusiasm, for certainly in the orchard of dermatologic investigation most attractive fruit remains momentarily beyond reach. Without basic knowledge of etiology being as yet complete, the accumulation of experience is nevertheless such that one can do much to relieve most of the patients who suffer from dermatoses of unknown cause Such knowledge is valuable and it has been hard won.

The order of presentation of this large group of clinical entities without regard to etiology which guides the classification of other chapters of the text, is arbitrary by constraint not by election. I chose to place descriptions in sections possessing some degree of morphologic coherence, grouping dermatoses of undetermined cause as well as possible according to their principal characterization as (1) erythematous, (2) eczematous, (3) scaly (4) bullous, (5) sclerotic and (6) atrophic.

Morphologic classification of dermatoses is obsolescent One looks forward to the predictable attrition of this chapter as its descriptions are in the future removed one by one to other locations in the book. The day will come, I may suppose when such a chapter as this no longer appears in a text on dermatology

ERYTHEMATOUS DERMATOSES OF UNDETERMINED CAUSE

ERYTHEMA

The initial stage of inflammation is manifested by capillary dilation, clinically visible as redness, or erythema. The color is blanched by diascopic pressure. If the cause of hyperemia acts over a period of time with considerable intensity exudative changes occur Hyperemia may be active or passive the former being inflammatory erythema the latter representing venous stasis. Erythema may be due to the action of external agents, such as heat, cold and trauma and chemical irritants (erythema venenatum) Symptomatic erythema develops as a result of some internal or systemic cause affecting vessel walls. Cutaneous vasodilation is erythema which may exist as a temporary phenomenon of vascular activity such as blushing or as a permanent change in the vessels, such as port wine angiomas.

Erythema is recognized by pressing upon the lesion the color fades but returns promptly on release of the pressure a petechia is not blanched by pressure. The cause of an erythema may be indicated by its location, distribution duration and history when these are interpreted in the light of knowledge of possible causes.

Symptomatic Erythema may result from physical or chemical agents acting on the skin producing vasodilation and so, redness, which disappears under diascopy Systemic diseases of many varieties and other derangements of the general economy which may be labeled intoxications, for want of a better term may also cause erythema. Allergy is perhaps the commonest factor for foreign proteins, serums and medicines frequently give rise to roseolas. Local asymmetric distribution speaks for a local instigation of the symptom and symmetry and widespread distribution are features of erythemas of internal origin. Neurogenic erythemas as varied as blushing the dependent cyanosis of psychoneurosis, and vasodilation following sympathectomy may

be mentioned. The erythema of contact dermatitis is pruritic, while other erythemas are generally practically asymptomatic. The pathologic changes are usually completely reversible.

Erythemas symptomatic of systemic disease are seen in typhoid fever: rose spots, sparse and small on the abdomen especially; in syphilis: the roseola; in diphtheria, gonorrhea, meningitis, rickettsioses, streptococcic and staphylococcic infections (q.v.) various rashes.

INFECTIOUS MONONUCLEOSIS is an acute i fectious disease occurring usually in young people and characterized clinically by malaise, fever and lymph node swellings. The blood picture and agglutination test are characteristic. The typical case begins with sore throat malaise and aching fever and sometimes nausea and vomiting Lymphadenopathy is generalized, but the cervical nodes, particularly those in the posterior triangle are most commonly involved. The spleen is usually enlarged. Fever is generally moderate and may last from a few days to several weeks. Some cases of mononucleosis present initial leukopenia, rising temperature enlarged spleen abdominal pain, and a rash suggesting rose spots. Such cases may sometimes be co fused with typhoid until further laboratory wo k confirms the diagnosis. Complications practically never occur Convalescence varies greatly and may be prolonged and characterized by weakness. There is another type of glandular fever in which the onset is more in idious, the symptoms are less acute a d the febrile period and lymph node enlargement more prolonged.

In infectious mononucleosis the transient rash may resemble German measles (Contratto AIntM 73: 449 1944) or may be scarlatiniform (Halcrow et al.: BMJ : 441, 1943) According to Templeton and Sutherland (J 118: 1 15 1939) the rashes are generally of a fine macular character with perhaps slight papulation. The trunk is most often involved, the facial region a close second. Of 1 instances observed, 1 were like German mea les the remainder less characteristic consisting of multiform lesions or of slight erythema on the face or abdomen Itching is mild or absent. The eruption appears at no particular period in the course of the disease being seen anywhere between the third and the twentieth day lasting for from 3 to 7 days and fading without desquamation They quoted Tidy (Lancet 2: 180 236 1934) a having described * importa t types of eruption (1) a macular eruption in the febrile type and ( ) a rubelliform eruption, mainly in young children. In the febrile type in the English 1930 epidemic the rash was a prominent feature and present in the majority of cases. It usually was referred to a maculopapula or roseolar eruption. It i rare in childhood. In the ordinary course it fades before l mph nodes become palpable; this is almost invariably so in adults. The rubellif rm eruption occurs mainly among oung children. It may appear at the onset, before or with the glandular enlargement or later in the att ck As in rubella, the erupt on may be confluent in some parts a d discrete in others, and the occipital odes are frequentl nlarged. Frupti ns may develop which have been described rticarial, rythema nodos m like or morb lliform. These are usually transient. Herpes labialis, although it has been recorded many times, i seldom seen in the ordinary glandular case.

Seve e angina, with purulent exudate, edema a d hemorrhage has been described in fectiou mo nucleosis (Smith and Shaw BMJ 1 581 1945) The presenting complaint wa *a painf l preputial ulcer with large inguinal nodes* in the case of Kallos (ADS 69: 018 1954)

SEPTICEMIA.—Rose spots erythematou plaques, and erythema multiforme like and emboli lesions are seen. Petechiae i septicemia are often toxic rathe than embolic (R binson UCutRev 1937 p. 490) U rticarial, purpuric and pap lopust lar rashes well as rythematou scarlatinif rm and desquamative eruptio s occur Staphylococcic septicemia n the puerperium ca sed acute pemphigus (q v) in a woman whose autopsy was reported b Rob nson (CalifWM 45 407 1936) Septicemia due to *Gaffkya tetragena* caused co flue t macules of the face nd rubella l ke eruption noted by Bl ks et al. (QuartJM 10 1 1917) A recurrent m b ll form urt carial exanthem occurred in ch ld with Pf iffer bacill infect on (Leichte tritt and Schober KlinWchn 1029 19*4) Rashes in pneumococcu sept cemia were reviewed by Willard (DZtschr 70: 2*1 1935) Rose spots, late becoming blotchy on the dorsa of th hands and fore rms, spreading generally when the pat ts became moribund, occurred in fatal cases of salmonella infection reported by Schwabache et al. (BMJ : 353 1943)

BACTERIAL ENDOCARDITIS.—Crops of petechiae occur in some 80% of the cases (Libman MedClinNoAm 117 1918) and emboli account for these a well for tender c taneous nod les in luding those wh ch a e designated as Osler s nodes. These are reddish swellings pea t almond size with whitish centers, lasting only a day o so, located in the pads of the fingers and toes, th the a and hypothe r eminences, the sides of the fingers and kin of th fo earm seen n 7 of 10 patients with chronic bacterial endocarditis observed by Osler (QuartJM 19 1908) Libman described also the tired look, the brown pigmentation of the face the d rty yellow color of the skin and the occasional d rk red, papuloerythematous rupt on the bridge of the ose a d mala areas. Weiss (JMtSinaiH, 1942 p 1079) recorded his personal experience with the disease almost to the time of his death.

LEPTOSPIRA INFECTIONS of various kinds, including Weil s disease and relapsing fevers, may be accompanied by rose spots resembling those of typhoid feve on the trunk and limbs especially during the period of onset (Gillespie: J 104: 1878, 1933) In canicola fever a spirochetosis resembling Weil s disease and characterized by abrupt onset, rigors fever severe headache, photophobia, muscle tenderness and meningeal irritation, m rbilli form or scarlatiniform rashes lasting only for a day or two occur (Edit: BMJ 1 239, 1950) *Leptospira pomona* infection, curable with Chloromycetin, is rather similar and sometimes causes transient maculopapular rashes (Lerner a d Lindsay: SouthMJ 45 1177 1952) In an unidentified but be ign infectious disease of acute onset with fever lymphadenopathy splenomegaly and leukope ia with relative lymphocytosis occurring i the spring and fall in adult patients mainly Blake et al. (YaleJBiol&M 14 573, 1942) observed a red-brown maculopapular eruption.

MISCELLANEOUS INFECTIONS.—In influenza, small white specks on the buccal mucosa may be seen d ring the first few days (Wolff: APediat 58 1 1941)

In pappataci, a generalized rash combining features of urticari and erythema multi forme in some cases, or blotchy erythema about the sebaceous follicles low i the axillary and lateral thoracic regions, was described by Sabin et al. (J 125 603; 693, 1944)

In pretibial feve a curious epidemic f brile disease of abrupt onset with myalgia, splenomegaly bradycardia and leukopenia, th striking manifestation was an erythema tous ra h, solely or predominantly pretibial in distribution, appearing about the fourth day (Lipscomb and McMahon: J 128: 90 1943)

In psittacosis a exa them consisting of minute, somewhat thickened, pearly spots was described by Averbach and Ink (abs J 130: 726 1945)

The eruptions in heumatic fever are described unde the titles Erythema marginatum (q.v) and Rheumatic nodules (q.v)

In toxoplasmosis symptomatic erythema may be maculopapula nd ge eralized (Pinkerton and Henderson: J 116: 807 1941)

AVITAMINOTIC STATES may exhibit erythema—pellagra, for example; and rashes in diabetes mellitus are probably of this nature (Rudy and H ffman: NEngJM 227: 893 1942)

CAISSON DISEASE is causative of symptomatic erythema. Pruritus or formication may be the first and only symptom noted, but lividity and marbling sca latiniform rashes and ven petechiae are sometimes seen. Marmoration affects the extremities more than the trunk, is dark blue, and is accompanied by swelling at first, but later it entirely disappears. The kin lesions have been called sandboys itch (J akinson: BritJSurg 27 6 1940) apparently caused by emboli of nitrogen bubbles (Aldso: be BJD 62: 271 1950) See Mellinghoff (ZtschrKlinM 127: 437 1934); Schilling (USNMB 36 235 1938)); Koenig (MunchMWchn 86 370 1939)

CANCER.—See Skin manifestations associated with internal ca c r

CARBON MONOXIDE POISONING.—Generalized cyanosis flushing is more commonly seen than a cherry-pink skin. Circumscribed erythema, roseola, vesiculation or ecchymoses may occur (Meigs and Hughes: AIndustHyg 6: 344 195?) A bullous ruption on the dorsa of the hands, becoming hemorrhagic and suggestive of acute pellagra, occurred following an attempted monoxide suicid (Weber: DWchn 127: 175, 1933)

X-RAY THERAPY is sometimes followed by a generalized maculopapular exanthem, which, in the 4 cases reported by Loewe and Camiel (AmJRoentg 43: 537, 1940) occurred fter radiologic treatment of c nce of the mouth. The macules on the face became confluent, vesicular hemorrhagic scaly d crusted about 8 days after radiation, and th patients were severely toxic. Itchy erythematous and papular rashes were noted after rradiation f the thyroid and pit itary glands in several cases by Bray (BritJRadiol 12: 31., 1930) Erythema multiforme sometimes follow x ray therapy (Davis and Pack: ADS 66: 41, 1952) as may herpes zoster (Schmitt and Thierfelder: Strahlenthe 93 417 1934) Severe pruritus followed by a generalized bullous eruption was seen in patients afte they received large doses of x-ray therapy reported Marzini and Biasi (abs YBD 1954 p 59)

PANCREATITIS.—In acute pancreatitis, livedo reticularis occurred in the patient of Sigmund nd Shelley (NEngJMed 251: 851 1954) Other changes that may appear include, they noted morbilliform ruptions, cyanosis, jaundice, greenish edematous patches and bluish discoloration bout the umbilicus.

POLYCYTHEMIA ind ces deep redness of mucous membranes and sometimes hyperpig mentation and ecchymoses. Acne urticata has been described in a umber of cases (Klauder: ADS 33: 145, 1935; Weidman and Klauder: ADS 39: 643, 1939) As noted by Kaposi (AfDeS 26: 57 1894) this eruption is composed of pale red elevated, wheal lik papules of small size, with summit vesiculation, soon excoriated, appearing in crops, generally first on the face later on the extremities, f voring the extensor surfaces and sim ulati g dermatiti herpetiformis. Lividity f th kin and a diffuse eczematoid eruption with da k reddish papular lesions, scars and pigme tatio w re seen in the case of Rostenberg (ADS 41: 807 1940) Erythroderma and angioneurotic edema affecting the legs

occurred in that of Torrey (ADS 43: 870, 1941) Koilonychia was described by Glazebrook (EdinMJ 2: 65 1944) Papular urticaria was the feature of the case of Strickler (ADS 52: 173, 1945) who found records of 13 similar ones. Pruritus may be a conspicuous complaint (Brumpt: PresseM 60: 1307, 1952) and in obscure cases of widespread itching polycythemia must be considered. Jaundice and vascular thrombosis also occur (Sohval: AIntM 62: 925, 1938)

Erythema ab Igne.—See Burns.

Erythema Arthriticum Epidemicum.—See Rat bite fever

Erythema Caloricum.—See Burns.

Erythema Induratum.—See Tuberculosis.

Erythema of the Ninth Day—See Dermatitis medicamentosa, arsenic.

Erythema Pernio.—See Frostbite

Erythema Streptogenes.—See Pityriasis streptogenique.

Erythema Traumaticum results from slight wounds or similar injuries friction, and pressure and rubbing such as that excited by ill fitting trusses and the like.

Erythema Venenatum is produced by the action of vario s mineral and vegetable poisons, such as sulfur alkalies, mustard, cantharides, pyrogallic acid, rhus and other plants. Dermatitis venenata (q.v) is erythematous if mild, and is erythematous at first.

Erythrocyanosis.—See Frostbite.

Erythromelalgia.—See p. 808.

Livedo Reticularis.—See Frostbite.

Stocking Erythroderma.—Striking instances of bilateral, symmetric erythema of the feet and legs were reported by Hartston (BJD 41: 105, 1929) He believed them to be of psychosomatic origin. Compare Erythromelalgia.

Rheumatic Disease—ERYTHEMA MARGINATUM is the most typical of the cutaneous manifestations of rheumatic fever in which there occur diverse eruptions, including erythema multiforme petechiae, urticaria and erythema nodosum (MJAustral 14 461 1940) In erythema marginatum, there occur asymptomatic pinkish circular and crescentic patches migratory and evanescent. Also known as Erythema Annulare Rheumaticum of Lehndorff Leiner the superficial semicircles and rings may signify severe involvement and liability to cardiac damage wrote Urbach and Bleier (ADS 41: 515 1940) although Campbell et al. (USNMBull 46 360 1946) considered this urticaria like eruption of less serious prognostic import. The rash disappears without pigmentation or scaling In children with rheumatic endocarditis, Abt (AmJ MedSci 190 824 1935) described the pale red or bluish expanding rings as occurring on the chest abdomen thorax and back, but not on the extremities, face or mucous membranes.

RHEUMATIC NODULES.—The ephemeral type consists of pea to hazelnut sized painless nodes commonly occurring on the forehead. Usually however the node is a small subcutaneous tumor over which the skin slides smoothly Hard, elastic movable generally painful these may resemble gummas or exostoses. They are of pea to almond size stationary for days or weeks, dwindling and disappearing in one or two months. The usual locations are near the joints, especially the elbow knee, wrist and ankle, and in fibrous tissues investing bones located subcutaneously such as the iliac crest, scapula, forearm, and frontal and occipital bones. They are symmetrically disposed, as a rule isolated not confluent, and from 1 to 60 in number, and are pathognomonic of rheumatic infection according to Hayes and Gibson (J 119 554 1942) Inflammatory nodules, deep-seated and connected with fascia, tendon or periosteum in cases of severe rheumatism, have been described. Painless, bluish nodules on the extensor surfaces of the extremities along with maculopapular and purpuric lesions have occurred in cases of acute rheumatic fever

See Keil (Med. 17 261, 1938) Sweitzer and Winer (ADS 45: 315, 1942) described fibrotic nodules in general Juxta-articular nodules (p. 404) are seen in yaws and syphilis. See also Erythema nodosum (p. 845)

Subcutaneous nodules in poliomyelitis and erythrocyanosis, affecting the lower half of the legs, were discussed by Telford ADS 36 952, 1937) Histologic differentiation of nodules of rheumatoid arthritis from those of rheumatic fever is plain, according to Bennett et al. (APath 30 70 1940) Weber (BJD 55: 1, 1943) found foam cells in the nodules of his 3 arthritic patients, who were helped by a low fat diet.

Heberden s Nodes are tender firm bony outgrowths of insidious onset in persons of middle age at the sides of the distal interphalangeal joints of the fingers in primary osteoarthritis (J 119: 852, 194) Toes are not similarly affected. The nodes are 10 times as common in women as in men (Stecher and Hauser: AmJRoentg 59 326, 1948) As an



Fig. 1038.—Erythema annulare rheumaticum. (Dr Arth r F Abt, from W ener: Skin Manifestations of Int rnal Disorders, Mosby 1947)



Fig. 1039 —Rheumatic nodules. (Wiener Skin Manifestations f Internal Disorders, Mosby 1947)



Fig. 1040 —Heberden's nodes.

idiopathic form of osteoarthritis of the finger joints Heberden s nodes are i dependent of other forms of osteoarthritis, obesity or hypertension (Stecher et al.: AmJHumanGenet 5: 46, 1953) but they are related to menopause occur only when innervation of the hand is normal, and are inherited as an utosomal, sex influenced trait, dominant in women, re-

cessive in men. X ray examination shows narrowing of joint space irregularity and spurs arising from the bones about the terminal joint. In early cases small islands of bone can be recognized in extensor tendons near the distal phalanx.

Erythema of the Palms with diffuse or blotchy redness due to arteriolar dilation is seen in portal cirrhosis (liver palms) chronic gastrointestinal and pulmonary disease rheumatoid arthritis malnutrition and pregnancy (Perera: J 119 1417 1942; Lofgren: ADS 46: 503, 194.; Ratnoff and Patek Med 21: 207 1943) Palmar erythema of a peculiar type affecting especially the volar eminences and without symptoms, as described originally by Lane (ADS 20: 445 19*9) was discussed by Walsh and Becker (ADS 44: 616 1941) who called attention to its association with spider nevi and its onset during pregnancy in 4 of the 20 collected cases. In a review of the literature, to which he added 11 cases, Bean (AmHeartJ 25: 463 1943) noted that all patients suffered from pulmonary or hepatic disease or both, and that skin manifestations varied in degree paralleling that of the visceral disease. Vascular spiders frequently accompanying this erythema he at tributed to, possibly the protracted increase in circulating 17 ketosteroids, of which there is an excess in pregnancy and also in states of impaired li er function, for the liver destroys or inactivates estrogenic substances. See Bean et al. (SGO 88: 39 1949) also Telangiectasis.

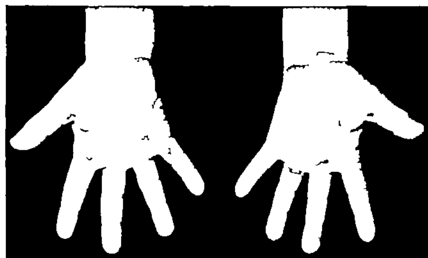


Fig 1041 —Erythema of the palms, cause undetermined, in a healthy girl 11 years old (Dr J Lamar Calloway)

Erythema Nuchae.—Transient erythema affecting the occiput and nape of the neck in newborn infants, asymptomatic and doubtf lly related to macular hemangioma, was bserved by Bettley (BJD 52 363, 1940) as a common disorder occasionally seen lso about the e lid and forehead. It is not related clearly if at all to pressure on the fetal head. It does not require treatment.

Dermatitis Colonica is manifested by macular ovoid erythematous lesions occurri g on the abdomen thighs and rms of person with bowel troubles, whose stools show ex pt onal proport ons of streptococci (Whitfield BJD 44: 4 1932) The borders of the patches a e made up of almost discrete, flat, red macules. Fine chapped scaling may be prese t and telangiectasis may be discerned. The lesions are a ymptomatic. Glaze (South MJ 29 909 1936) called attention to similar lesions. Almost asymptomatic tinea ersi color (q v) mu t be differentiated, and also the seborrheids occurring in seborrheic derma titis (q v) I have yet to see a case of Whitfield s disease

Papular Petaloid Erythema wa the title given by Civatte et al. (BsocfrançD 44: 334 193) to a rash seen in 4 patients, otherwise healthy whose early lesion occurred in ax rticular fold, then spread to involve the tru k and extremities. They were num rous on the flanks, abdomen and front a d s des of the thorax, spari g the back face, a d hand and feet. The lesions were tiny sharply marginated, and rosy in color becoming flat and undergoing slight desquamation on evolution. Pruritus was present in all cases. At pl cal pityriasi rosea would be difficult to distinguish from thi condition.

Epidemic Eosinophilic Erythredema was observed by Klopstock and Steinitz (J 129: 144 1945) in pat ents seen in Palestine who manifested cut eou swellings, usuall red and hot like erysipelas occasionally urticarial or erythema nodosum like. Persisting for o ly a few da s, they migrated over wide areas of the body a d swelli gs might continue to appear constantly or intermittently o er a period of weeks or months. Eosinophilia ranged generally from 15 to 35% of the total white cell count of from 1,,000 to 15,000, and aching pa o malaise fte occurred. Feve was bse t or low but the disease while partially in pacitati g was not severe. The possib lity that it might represent filariasis was considered b t ot proved. Trichiniasis could cause such phenomena.

Riley Day Syndrome.—Blotchy erythematous macules of 1 to 2 cm. diameter occur on the face especially and the skin is cold and damp in cases of this bizarre disorder, which appears to represent a familial autonomic dysfunction (Mintz and Rubin: ADS 67: 561 1953) Described originally by Riley et al. (Pediat 3: 468 1949) the syndrome occurs in Jews and is manifested with defective lacrimation, skin blotching, hyperhidrosis, drooling emotional instability motor incoordination, hyporeflexia, cyclic vomiting relative indifference to pain hypertension, reduced resistance to infections, mental retardation, convulsions and corneal ulceration. Some 33 cases were collected by Riley (J 149: 1532, 1953)

Erythema Scarlatinoides.—Under this heading may be grouped a number of ill-defined conditions which may result perhaps from a variety of causes and are characterized clinically by scarlatiniform redness and desquamation. While the redness and exfoliation differ considerably in degree the constitutional symptoms throughout the course of an attack are as a rule remarkably trivial. Attacks of erythema scarlatinoides are generally ushered in by chilly sensations and feelings of malaise followed by a rise in temperature (from 99° to 101° F) which may persist for 2 or 3 days The eruption develops in from 24 to 72 hours. Pinkish in color and somewhat mottled at first, it soon becomes bright red and of more or less general distribution. The fever and other constitutional symptoms usually abate at this time There may occur mild itching and burning and the patient may complain of a feeling of tenseness in the skin but symptoms are never a prominent feature of the disease. Desquamation, commonly in the form of large thin translucent flakes, commences early even while the rash is spreading and continues for a week or longer On the scalp the eyebrows, the beard and the mustache the scales are fine furfuraceous, abundant and adherent. In some instances, the palms and soles appear as if covered with a thick layer of collodion and the exfoliation may bear a striking resemblance to the glovelike desquamation of scarlet fever Rarely the nails exfoliate and more or less hair loss occurs.

Recurrences are likely either immediately following an attack or at intervals of several weeks or months. Sutton, Sr., observed a young woman whose rash recurred at about the same time each autumn for 4 years. One of Crocker's patients had 5 attacks in 7 years, and Tilbury Fox recorded an instance in which the recurrences were even more numerous. Grindon (ADS 2 623 1920) reported an interesting and ultimately fatal example of the frequently recurring type.

The disease is perhaps toxic in origin due to any of several causes. Brocq (JCutVD 3: 225, 1885) was of the opinion that dry-skinned persons are more susceptible to it Little is actually known. I was unable to unearth fact re l a case I studied during 1936 although food idiosyncrasy focal infection, dermatitis medicamentosa and sources of dermatophytid were sought. It is not likely that true cases of erythema scarlatinoides are dermatitis venenata, although resemblances may exist. Atropine and mercury can cause such rash (see Dermatitis medicamentosa)

The only disorder with which the disease is likely to be confounded is scarlet fever From this it is to be distinguished by the short prodromal period, the absence of severe constitutional and pharyngeal symptoms the early and abrupt commencement of desquamation and the tendency to recur

DECIDUOUS SKIN, reviewed by Bechet (ADS 37: 266, 1938) is to be differentiated from erythema scarlatinoides, as is also keratolysis (q v., probably a dermatophytid) Deciduous skin is the continuous periodic or seasonal shedding or peeling of the epidermal layer of the skin of more or less general distribution. The palms do not scale. The shedding continues throughout life I surmise that this is the form of congenital ichthyosiform anomaly a case of which was described by Fox (ADS 3: 202, 1921) as keratolysis exfoliativa congenita, although in this woman peeling was perennial rather than seasonal. See Ichthyosis p. 1037

THE EXANTHEMATOUS FOURTH, FIFTH, AND SIXTH DISEASES

Dukes Disease (Fourth Disease Parascarlatina) is a mild exanthem occurring in children. Premonitory symptoms are slight with or without sore throat Glossitis is absent. The affection is seen usually in the spring or summer months. The incubation period is said to be from 9 to 21 days. The eruption is bright, rosy red, and slightly edematous but not hot to the touch.

Figs. 1042 and 1043.—Erythema infectiosum. Prairie Village, Kansas, epidemic of May 1961.



Figs. 1044 and 1045.—Exanthem subitum. (Dr. L. H. Barenberg.)

It may cover the body within a few hours. Lymph nodes became large and tender Fever rarely reaches 104° F Desquamation follows. There is no cross immunity with German measles. See Dukes (Lancet 2: 89 1900) Traisman (IllMJ 49 495 1926)

Erythema Infectiosum (Fifth Disease Ringelröteln Megalerythema) — This feebly infectious disease, characterized by its rash but otherwise practically without symptoms, has been reported from scattered parts of the world It occurs in epidemics, is a disease of early childhood, appears in the spring and summer and produces no cross immunity with other exanthemas. Determination of the cause has baffled every investigator Kerr and Marsh (AmJ PubH 23 1271 1933) reported an epidemic of 25 cases in 11 weeks at Elmsford N Y The incubation period was 4 to 14 days. The epidemic in a New York orphanage described by Chargin et al (ADS 47 467 1943) comprised 170 attacks in 80 patients among the 137 children The eruption is maculopapular rose red and more pronounced on the face, legs and arms. It appears first on the cheeks and may be limited to this location (Rector JPediat 15 540 1939) The lesions are peculiarly circular and crescentic. They enlarge peripherally undergo confluence heal in the central zone and so produce a geographic annular and angularly mottled appearance that is quite striking The skin is swollen and warm but does not itch. The patient s temperature may rise to 101 rarely Mild leukopenia may be found. There is no adenopathy or splenomegaly The eruption disappears in about 4 days, leaving no scale scar or pigmentation. Treatment is unnecessary ordinarily although aspirin aluminum acetate baths and a bland ointment might prove alleviating

An epidemic exanthem seen in Boston in the summer of 1951 with apparently unique features was described by N va et al. (J 155: 544, 1954) Most of the patie ts were young children. Fever was low and of only a few days d ration. Discrete, sparse, faint pink, maculopapular lesions of the skin were noted, the rash seldom attaining the severity of fio ld measles. The face and upper chest, often the arms, buttocks and legs, were the sites of its appearance soon after other symptoms had subsided. A few children showed sparse, herpetoid oral lesions. The disease was relatively trivial in most of the patie ts. The description suggests atypical fifth disease.

See Shaw (AmJMedSci 129 16, 1905) quoting original recognition by Escherich in 1896, Radaeli (also BJD 32 82, 1920), Italian cases Herrick (AmJDisChild 31 486, 1926) 74 cases from Cleveland Smith (APediat 46 464, 1929), 14 cases from Ogden; Lawton and Smith (AIntM 47 28, 1931) etiology undetermined in Connecticut cases, color plate; Coe and Kelly (CalifWM 36 30 1932) Berkeley cases; Cowern (MinnM 16 628, 1933) 10 cases without lesions of face or coryza; Judd (ChinMJ 48: 62, 1934), Chefoo epidemic; Orgler (KlinWchr 15: 789 1936) Fox and Clark (AmJDisChild 73 461, 1947) Milwaukee cases Edit (BMJ 2 870, 1950); Korting (DWchr 124: 708, 1951); Phillips (ADS 67: 618, 1953 SouthMJ 47: 383, 1954) Tennessee cases, questionable transmission by bird mites.

Exanthem Subitum (Roseola Infantum Sixth Disease) is a mild disease affecting principally children under 3 years of age It may be sketched as a 3-day fever syndrome with morbilliform rash, leukopenia mononucleosis and a favorable outcome (Rosenbuch abs YBD 1940 p. 188) Most cases occur during the fall, with some in winter and summer The incubation period seems to average about 10 days, but infectiousness is not great. The onset is acute with a temperature of from 102° to as high rarely as 105 F., accompanied by evidences of upper respiratory infection and tonsillar and pharyngeal congestion. The child is irritable but not toxic. In some of the patients of Barenberg and Greenspan (AmJDisChild 58 983 1940) fever was highest at first and f ll by crisis, while in others the maximum was reached on the second day and fell gradually The rash is rubelliform affects the whole body is discrete on the trunk and tends to be confluent about the neck. It appears at the time of fall of temperature about 4 days after the initial symptoms of illness. At this time there are lymphocytosis and usually mild leukopenia. Lymphadenopathy is not present as a rule a distinction from rubella. Complications are extremely rare; the disease is relatively trivial the rash fades in 2 days or so. Symptomatic treatment with aspirin a barbiturate and phenolated calamine lotion suffices.

See Jones (AmJMonth 64 401 1939), 68 cases Jennings (JMSocNewJersey 37 377 1940) 66 cases Greenthal (WiscMJ 40 23, 1941) 100 cases Rudolph (FlaMAJ 27 547 1941) Abrams (AlaSMAJ 12 112, 1942), Derenberg et al. (NEngJM 241 262, 1949) 151 cases, Windorfer (DMedWchn 9 1201 1934) 117 cases seen in 4 yrs peak incidence in second half of first year convulsions common at onset, pharyngitis usually present; McQuitty (BMJ 1: 1005, 1955) 12 British cases.

ACRODYNIA

The Pink Disease, Erythredema and Swift's Disease are synonyms for this rare disorder of infants. The onset is insidious with loss of weight anorexia, and listlessness. The basic symptoms comprise a profound change in temperament muscular hypotonia and tachycardia according to Fisher (BMJ 1 251 1947) The hitherto thriving infant loses his normal contented disposition and gradually comes to present a picture of unhappiness far exceeding in intensity and duration the intermittent fractiousness of teething to which process the symptoms of the disease are at first too readily ascribed Unhappiness increases until he exhibits a continuous, miserable peevish resentfulness or an active militant fury against all the agencies of the external world. Muscular hypotonia may be extreme. Walking if attained is lost. The infant slumps spinelessly in the mother's arms with its face buried in her shoulder The thigh muscles especially lie flaccid and feel as if semifluid. The pulse ranges from 144 to 168 or even higher when the child is provoked. Cutaneous symptoms are variable In classic cases, the hands and feet become swollen, painful and itchy cold and clammy and pink or dusky red. Perspiration is excessive and a pruritic sudaminal eruption crisscrossed with excoriations may be found on the trunk and limbs The rash may be transient or may persist for weeks. Sweating gives the skin a moist cold, flabby, almost reptilian feel. Desquamation appears from 2 to 3 weeks later and its intensity parallels that of the rash Buccal and conjunctival irritations are manifested by refusal of food and photophobia with perhaps no external findings or only mild evidences, or quite troublesome inflammation. Secondary infection may cause ulcerative stomatitis, sloughing of gums, or bronchopneumonia which caused 7 of the 9 deaths in Fisher's 65 cases. The deciduous teeth may fall out. Gangrene of the extremities complicated the disease in 2 cases reported by Gadrat et al. (abs J 113 2097 1939)

Diagnosis.—Cobb (AmJDisChild 46 1075 1933) listed the 5 P's pinkness, photophobia peeling paresthesia and perspiration. He stressed also the features of sweating lacrimation, salivation, loss of hair tachycardia and hypertension.

Etiology—The evidence is strong that mercurial sensitivity is actually the cause The death of a British infant from the pink disease was accepted at a coroner's inquest as being accidental and due to hydrargyrum cum creta (Foreign Letter J 158 137 1955)

Neurologic infection, toxication and nutritional deficiency have been suspected. There is no seasonal or racial predilection. The peak age of incidence is 9 months and fewer cases are found after 18 months. Resemblance to ergot poisoning was noted by Debré and Névot (abs J 11 1772, 1939) Insomnia resembles that of encephalitis (Groom RockyMtMJ 38 616 1941) Similarity to the disease developing in young rats on diet adequate in vitamins but providing only egg white as the source of protein was noted by Findlay and Stern (ADisChild 6 1, 1929) and feeding raw liver appeared to be curative in 4 of their 5 patients.

The infants reported by Elmore (Ped 1: 643 1948) and by Bivings and Lewis (J Pediat 32 63 1948) had received calomel prior to the onset of the pink disease and they responded favorably to BAL. Urinary mercury ranged from 14 to 4000 micrograms per liter in 16 cases seen by Epstein (BMJ 2 1178 1950), who noted the common mercurial content of teething powders popular in South Africa and who obtained encouraging results with BAL in 4 cases. Swallowing ammoniated mercury ointment appeared to be the cause of the disease in cases (Silverman and Cassady NEngJM 247 343, 1952) Patch tests proved mercurial hypersensitivity the patient of Peters (abs J 14? 9 1 1951) child known to have received calomel. Close association between mercury and acrodynia was adduced in 13 cases by Dathan (BMJ 1 ?4 1954) who believed that calomel should be included in the poisons list.

At autopsy Warthin (APath 1 64, 1926) found extreme edema and slight meningeal irritation of the central nervous system, bronze erythema of the skin with hyperkeratosis and changes due to terminal respiratory infection or gastroenteritis to him these abnormalities recalled the changes in pellagra. Confirmation of the finding of neurologic

lesions was made by Wyllie and Stern (ADisChild 6: 137 1931) who performed autopsies on 7 cases, by Wolf et al. (JPediat 4. 493 1934) and by Péhu et al. (JNourrisson 23: 32, 1935)

In each of 6 cases studied psychiatrically by Leys and Cameron (BMJ 1: 191, 1952) there were indications that the child suffered from emotional deprivation and that the mother was in psychiatric ill health at the time the child s illness began.

Treatment requires good nursing good body hygiene, patience in feeding mild sedation and topical soothing A high vitamin intake is generally urged but it was the addition of nicotinic acid that seemed effective in the patient of Jahr and Dornberger (NebrMJ 24: 391 1939) Large amounts of B_1 and of wheat germ were recommended by Forsyth (MJAustral 2 751 1939 1 78 1941) Injections of B_1, inadequately absorbed by mouth, appeared curative to Durand et al. (JPediat 14 74 1939) The use of BAL (q v) must be considered. Exposure to mercury was demonstrated in 38 of 41 children with acrodynia studied by Warkany and Hubbard (AmJDisChild 81 335 1951) but BAL seemed ineffectual, possibly because the intoxication was already of long standing when it was commenced. Injections of desoxycorticosterone on 8 successive days proved dramatically beneficial in a child treated by Murray (BMJ 2 1116, 1950), confirming Brauer (BMJ 2 1003 1050) Its effectiveness was denied by Macdonald and Callow (MJAustral 1 363 1951) in a careful study of adrenal function in a controlled series of cases (see Edit BMJ 1 933 1951) Hypofunction of the adrenal cortex was thought causative at least in part by Hicks (BMJ 2 317 1951) who advised treatment with cortisone Priscoline appeared significantly palliative stated Gillespie (Canad MAJ 67 418 1952)

See Wood (MJAustral 1 145, 1937), description Edit (Lancet 2 540 1931) no cases prior to World W I, Penfold et al (MJAustral 2 127 1932) negati bacteriologic studies Braithwait (ADisChild 8 1, 1933) review Blackfan and McKhann (JPediat 2 44 1933) review 6 necropsies; Rocaz (The Pink Disease, Infantile Acrodynia, Wood transl., Hopkinson, London, 1933); Rousseont d Lafon (RevfrancPédiat 11 372, 1935), capillaroscopic findings; Wood and Wood (BMJ 2 637 1935) description Tisdall et al. (JPediat 12 391 1938) failure of icotinic cid Ja ett (SoAfrMJ 12: 381, 1938) review Feer (SchweizMedWchn 69 873 1939) ecula manifestations Bastible (IrishJMSc 6 220, 1939), 2 cases nd review, Crawford (PaMJ 43 473, 1940) description; Cassand et al. (abs ADS 41 388, 1940), 3 utopsies, William et al (Lancet 1; 78, 1940) response to B_1 by injection; Herz (UCinRev 44 389, 1940) review, Stephen (MJAustral 2 124, 1940) benefit from B_1 injections; Craig (BMJ 2 773, 1940) description Cheek et l. (MJAustral 1 107 1950) 27 cases, sodium chloride metabolism

ERYTHEMA MULTIFORME

Symptoms.—Erythema multiforme is an acute inflammatory disease characterized by the development of reddish macules papules and vesicles with symmetric distribution. The lesions vary greatly in size and configuration and papular nodular vesicular circinate, marginate and iris clinical forms are recognized. Erythemato-papular types may be separated descriptively from the vesico-bullous ones (Keil AnnIntM 14 449 1940)

The sites of predilection are the sides of neck and face dorsal surfaces of hands and forearms, legs, dorsal surfaces of feet, and mucous membranes. The lesions are bright or dark red in color fading to a purplish or violaceous hue Symptoms are slight as a rule An attack seldom lasts longer than 2 or 3 weeks. The lesions develop quickly and the inflammatory process may be of sufficient intensity to convert papules into vesicles with serous or even bloody contents. On the absorption of effusion iris-like lesions are formed and these continuing to enlarge may coalesce with neighboring rings. Mucosae are often involved otological changes being sometimes of such prominence as to obscure recognition of skin changes (Howard and Wible Ann Otol 55 146 1946) Ocular complication is sometimes seen, with catarrhal or purulent conjunctivitis sometimes causing corneal ulceration (Koke A Ophth 25 78 1941) In all types the color entirely disappears on pressure Scarring is infrequent but can result from secondary infection. Cases with high, intermittent and prolonged fever occur and despite articular pains and a duration even of months the prognosis is favorable (Leopold AmJDisChild 59 1298 1940) The interrelationships of erythema multiforme and the syndromes of Stevens and Johnson, Reiter and Behçet postulated by Robinson and Tasker (CalifM 69 140 1948) and others, are discussed under the title Mucocutaneous Ocular Syndromes (p 842)

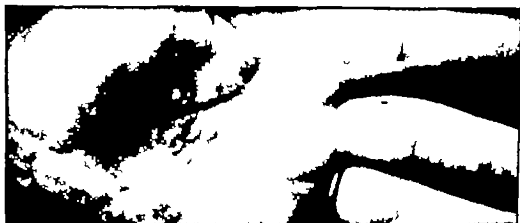


Fig. 1046.—Erythema multiforme showing iris lesions of palm.



Fig. 1047.—Erythema multiforme. (Dr. Max Jessner, from Wiener: Skin Manifestations of Internal Disorders, Mosby, 1947.)



Fig. 1048.—Bullous erythema multiforme such as phenolphthalein might cause. (Dr. J. E. Dienstaedt.)

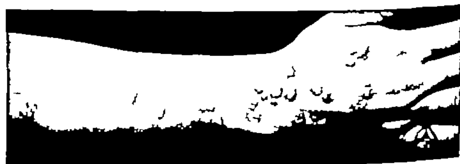


Fig. 1049.—Erythema multiforme.

Etiology—Numerous theories have been advanced to account for the causation. The cases of Osler (AmJMedSci 110: 629 1895 BJD 12 227 1900) manifested urticaria, angioneurotic edema, purpura exudative erythema, leukocytosis, splenomegaly fever arthritis colic, vomiting melena, asthma and emphysema, alone or in combination. Similar cases have more recently been recognized as allergic in nature (Stokes: MedClinNoAm 8 875 1924) Perhaps specific microorganisms are concerned, but findings are not uniform (Guy J 71 1993 1918) The disease occurs oftenest in the fall and spring A relationship to herpes simplex was discussed by Anderson (ADS 51 10 1945) Smallpox vaccination was apparently causative in the 3 cases recorded by Schwartz and Drainer (JPediat 29 512 1946) The similarities of erythema multiforme and erythema nodosum interested Noojin and Callaway (ADS 54 560, 1946) who stressed the coexistence of focal infection often streptococcic, in both conditions. Streptococcic infection was thought to be the specific cause by Welsh (JID 10: 401 1948) An accompanying pneumonitis without demonstrable parasitic cause was observed in the predominantly



Fig. 1049—Erythema multiforme, ulcerative and gangrenous lesions. Rare. (Dr Sam Sweitzer)

mucosal cases of Dingle et al. (AIntM 78 687 1947) Löffler s syndrome, with eosinophilia reaching almost 80% was described in association with erythema multiforme by Lehmann (SouthMJ 41 37 1948)

Pathology—Changes in the cutis are those of acute localized inflammation. In the papillary layer are vascular dilation, perivascular cellular infiltration and proliferation, more or less emigration of leukocytes and even of red cells, and edema. Collagenous tissue is swollen and transparent.

Diagnosis—The multiformity the bright or dark red color of the eruption, its symmetric distribution and predilection for the dorsal surfaces of the hands and feet and the sides of the neck the tendency to assume ring shapes, and the absence of itching are characteristic. The disease may be confused with urticaria which it occasionally resembles, but the rosy color and limited distribution of the lesions and their nonpruritic character together with the fact that they are never as transitory as those of urticaria, should prevent error Bullous cases are distinguished from pemphigus by their multiform character color and distribution.

Treatment.—Rest in bed is necessary in severe cases desirable in moderate ones. Foci of infection should be sought out and eradicated Sodium salicylate in large doses may help Sulfonamides have been curative in some cases. Small doses of Benadryl promptly relieved 2 patients of Pinkus (Ann Allergy 4 268 1946) Cortisone is often dramatic in palliation, as in the recurrent case of Schupbach and Gendel (ADS 64 783 1951) Various internal remedies, such as quinine salicin, potassium iodide and ergot have been recommended but are of dubious value Locally powders calamine lotion or aluminum acetate packs are indicated





Fig. 1051 —Erythema multiforme.
Fig. 1052 —Eruptive fever with stomatitis and ophthalmia. (Greenley AmJDisChild 49 1148, 1935.)



Fig 1053 —Eruptive fever with muco-ocular lesions. (Dr Charles C. Dennie)

See Hermann (InternatClin 4 122, 1910) visceral manifestations, Urbach (ZentralblHaut 46 412, 1933) herpes relationship Leipner (DWchn 100 1178, 1936) epidemic related to staphylococci infection Prakken (ActaD-V 17 133, 1936) bullous case followed by depigmentation Bruce-Jones (BJD 49 498, 1947), case recurrent from eating ice cream caused by casein Bregman (ADS 38 623 1938) a sulfanilamide cure Friedman (ADS 40 644, 1939) recurrent oral case Ustvedt (ActaMScand 131 32, 1946), clinical features, 219 cases Crawford and Leikart (J 140 780, 1949), unusual female with acute ulcerative colitis, spontaneously healing, Costello (ADS 67 226, 1953) eruption followed transfusion in Hodgkin disease Lynch (SouthMJ 48 279 1955) review and bibliography

MUCOCUTANEOUS-OCULAR SYNDROMES

Under this title, the syndromes of Stevens-Johnson Behcet and Reiter were reviewed and discussed by Robinson and McCrumb (ADS 61 539 1950) who judged that the pronounced similarities justify the belief that all three are variants of erythema multiforme exudativum,

Stevens-Johnson Syndrome.—This was originally described by Stevens and Johnson (AmJDisChild 24: 526 1922) on the basis of 2 cases resembling meningococcemia starting violently with fever developing a purpuric rash, manifesting conspicuous conjunctival and oral manifestations and resulting in blindness. Synonyms include Bullous Malignant Erythema Multiforme, Eruptive Fever with Stomatitis and Ophthalmia, Ectodermosis Erosiva Pluriorificialis, Dermatostomatitis, and Mucosal Respiratory Syndrome.

The striking picture was well described by Ginandes (AmJDisChild 49 1148 1935) Young persons, especially males, are the usual victims, more commonly during the spring season. The onset is abrupt with a temperature of 103 to 104 F., headache, chill malaise sore mouth and throat and frequently the symptoms of upper respiratory tract infection (Soll: AIntM 79: 475 1947) Vesicles appear on the lips, tongue and buccal mucosa; they become pseudomembranous lesions, with or without ulceration. Salivation is profuse. Conjunctivitis, rhinitis, balanitis and sometimes anal involvement of variable intensity accompany the oral and constitutional symptoms. Within a few days, erythematous macules vesicles and petechial lesions appear on the hands and feet and, to a lesser degree, elsewhere on the body The exudative lesions crust and heal in a period of 3 to 6 weeks. In 9 cases reported by 1933 only 2 were not totally blinded by the effects of the disease.

The course consisting of sudden onset rapid rise to maximum intensity and gradual return to normal, suggests violent, transient allergic or viral damage Ginandes patient presented dark, red oval elements, many of which developed necrotic centers, and persistent brown stains marked the sites of disappearance of inflammation the blood culture was sterile, as is usual Severe symptoms persist for little more than 10 days. Costello (JID 81: 127 1947) reported 33 cases 17 in detail, with 9 deaths and 1 necropsy; an upper respiratory onset occurred in more than half of his patients. Four cases were reported and the literature reviewed by Klauder (ADS 36 1067, 1937) who placed the syndrome with erythema multiforme and emphasized the variability of that disease. Lever (ADS 49: 47 1944) stressed the features of severity and eye damage despite the rarity of fatality Pneumonitis seems to be a part of the picture (Silver: AnnIntM 24 499 1946) Stanyon and Warner (CanadMAJ 53: 427 1945) described this mucosal respiratory syndrome and noted its gradual onset of 4 to 14 days, followed by suddenly severe symptoms, during which sulfonamides and penicillin were without value they suspected a virus cause. Four original cases and 77 from the literature were reviewed by Ashby and Lazar (Lancet 1: 1091 1951) who accepted the view that the diagnosis may be made in the absence of cutaneous lesions, as in disseminated lupus erythematosus also. Of the 81 cases, 69 were younger than 30 years of age 66 occurred in males, 7 showed corneal involvement and 6 of these were left with permanent visual defects (5 totally blinded) and skin eruptions were present in 67 Surgical emphysema was the unusual complication in a boy who recovered, reported Hahn (BMJ 1: 1321, 1953)

ETIOLOGY —Phenobarbital appeared to cause the disease in 2 cases reported by Berlin (abs YBD 1947 p. 160) It appeared following the administration of Tridione to an epileptic boy seen by Shaffer and Morris (Pediat 2: 30 1948) A virus resembling that of herpes simplex was recovered from the patient of Anderson et al. (ADS 59 231, 1949) Association with Vincent's disease, dysentery and sulfonamide allergy appeared significant in several cases of Thomas (BMJ 1: 1393, 1950) The cause is unknown.

TREATMENT —The patients of Walton (Lancet 1 214 1941) were relieved of chest symptoms but not of mucosal ones by sulfonamides, and transfusions seemed especially beneficial. Robinson (ADS 53 91 1946) attributed the sharp crisis in his patient to penicillin after sulfonamides had done no good. Cultures made from the eyes reveal *St pk. aureus* as a rule, often accompanied by streptococci, observed Goldfarb (JPediat 28: 570 1946) and vision has been preserved, he stated, only in patients who received adequate antibacterial chemotherapy Sulfonamides and penicillin prevented permanent eye damage in the cases of Wright et al. (AIntM 79 510 1947) Benadryl appeared to relieve the patient of Schoemperlen (CanadMAJ 56 73, 1947) Weisberg and Rosen (ADS 53: 99 1946) thought niacin, 100 mg t.i.d., beneficial. Aureomycin appeared to induce prompt resolution of the disease in cases of Lowenthal et al. (SoAfrMJ 24: 686 1950) and Harmston (RockyMtMJ 49: 931 1952)

There is a question of the dramatic value of ACTH (Wammock et al.: J 147: 637 1951; Agost et al.: NEngJM 46 219 195_), and of cortisone (Mecklin and Sanders NYSJM 5_: 1447 195_; Friedmann and Pathé: AnndeD 80 122, 1953)

Reiter's Syndrome comprises a triad of arthritis, conjunctivitis and urethritis not caused by known micro-organism (Lever and Crawford ADS 49: 389, 1944) It may exist when the triad is incomplete according to Hallande et al. (J 129: 593, 1945) Young males are affected and arthritis, usually multiple dominates the picture. When arthritis, with exacerbations, has existed for one or a few months urethritis and conjunctivitis appear These usually subside after a few weeks. Cutaneous lesions resembling those of keratosis blennorrhagica have occurred in some cases (Kuske: AfDuS 179: 53, 1939; Baxter: BMJ 2 833, 1946; Peters: ADS 50: 217 1949) Gonorrhea, however cannot be found, and despite the purulence of the disease sulfonamides and penicillin do not reliably influence it. The affected joints are red hot, swollen and tender but the condition is self limited generally clearing within 6 months. It is not rare, according to Pinck

(AmJMedSci 214: 76 1947) Recurrences may take place. The arthropathy of Reiter's syndrome does not result in ankylosis, while this may occur in keratoderma blennorrhagica or arthropathic psoriasis (Epstein: ADS 56: 191, 1947)

An inactivated emulsion of crushed lymph node tissue injected intradermally produced a tuberculoid reaction only in cases of Reiter's syndrome reported Storm Mathisen (ActaD-V 26 547 1946) a reaction analogous to the Kveim test.

Patients suffering from apparently this syndrome have been reported with bacillary dysentery (Herson: Marsh BMJ 2 ° 5 1946) A large number of cases was seen by Paronen (abs YBD 1948 p. 343) during an epidemic of Flexner's dysentery; two-thirds of the cases of Reiter's syndrome appeared within 11 to 30 days after the onset of dysentery as a sequel rather than a co comitant. A virus wa isolated from the patient of Dunham et al. (JUrol 58: 212, 1947)

The primary lesion was thought to be urethral by Bains (BMJ : 605, 1947) who reported that, while treatment was unsatisfactory yet urinary lesions cleared under neoarsphenamine. Mapharsen appeared to help the 3 patients of Khoury (JUrol 58: 268, 1947) Intravenou injections of gold benefited one of Willcox et al. (BMJ 1: 483, 1947) and Aureomycin appeared to cure the patient of Korb and Brown (ADS 62: 391 1950) who was unresponsive to sulfonamides and penicillin.

ACTH was followed by prompt and dramatic be efit in the 2 cases of Ogryzlo and Graham (J 144: 1239 1950) while cortisone induced remission of symptoms. The experience of Larson and Zoeckler (AmJMed 14: 307 1953) in 4 cases was similar

Behçet's Syndrome comprises a triad of genital ulceration oral aphthae, and uveitis or iridocyclitis in repeated attacks which, in later stages, are associated with hypopyon (Berlin: ADS 49 227 1944) Curth (ADS 54 179 1946) recognized formes frustes in which only genital or oral or eye lesions may occur Ocular symptoms may precede or follow other features of the triad; both eyes are eventually involved, and blindness is likely to result. Retinal and vitreous hemorrhages may occur (Katzenellenbogen: BJD 58: 161 1946) Cutaneous lesions appear in some cases including erythema nodosum and erythema multiforme-like acneic and papulopustular eruptions. The skin is markedly sensitive so that trauma provokes pustules, and erythema follows any injection.

The cause is not known, but Behçet (BSocfrançD 46: 674 1939) suspected a virus. Histologic examination has revealed nothing specific.

Treatment has been disappointing but focal infection should be eliminated, and sulfonamides, penicillin transfusions, and smallpox vaccination may yield benefit. Cortisone and ACTH disappointed France et al. (Med 30: 335, 1951) nor did any of many other treatment efforts afford substantial improvement. Yet the 4 cases treated with cortiso e o ACTH by Phillips and Scott (Lancet 1: 366, 1955) responded fa orably Vitamin K helped a case resembling Beh et's syndrome (Ambrose BMJ 1: 358, 1947)

See Baader (AfDuS 149, 261 1925) dermatostomatitis; Kumer (DMschr 72: 62, 1925); Rosenberg and Rosenberg (ADS 41 1046, 1940) Henry (BMJ 2: 373, 1942) Kove (AmJMedSci 210 611, 1947), Meakins (CanadMAJ 56 663 1947) mucosal respiratory syndrome Sneddon (BMJ 1 925, 1947) 6 cases Jonstone (Lancet 1 376, 1947) death with telectasis and subcutaneous emphysema Dresner (Lancet 2: 1036, 1949) penicillin no help; Patz (AOphth 43 244, 1950), Edit (J 146, 1424, 1951) riants of erythema multiforme; Dagett (AmndeD 79 149, 1952) review nd bibliography Reiter's syndrome Hall and Finegold (AnnI tM 38 563, 1953) 22 cases, Reiter' syndrome Friedmann and Pathé (AmndeD 69: 132, 1953) 2 cases Stevens-Johnson type Steel and Moffatt (BMJ 1 795, 1954) Stevens-Johnson syndrome caused by phenylbutazone.

ACRODERMATITIS ENTEROPATHICA

This rare disease of childhood, likely to prove fatal starts about the time the child is weaned, according to Danbolt (ActaD-V 28: 532, 1948) with pustular and psoriasiform eruptions on the face, perineum and limbs. The course is marked by paronychia, alopecia (eventually total) recurrent episodes of diarrhea, and progressive marasmus. The onset is insidious, with a small, localized skin eruption close to one of the body orifices or on an extremity wrote Dillaha et al. (J 15_ 609, 1953) The eruption is accompanied by, or shortly followed by loss of hair and gastrointestinal disturbances, chiefly diarrhea. The intermittant course is marked by increasingly more severe exacerbations, during one of which death terminates it. The little boy studied by Bloom (ADS 69: 516 1954; 70: 240, 1954) exh bited erythematovesicular scaly plaques over the Achilles tendons, sides of the heels, plantar digital skin of the toes, popliteal areas, knees, elbows, arms and forearms, intergluteal fold and adjacent skin of the buttocks, and the end of the penis. Nails were brownish thick and distorted with severe paronychia. Reddish and whitish spots were p esent on the buccal mucosa. The hair of the scalp wa thin and fuzzy Bowel troubles included diarrhea, discomfort and anorexia, and when they were worse the eruption was worse. Bloom thought the disease related to epidermolysis bullosa, the monilia probably secondary invaders. Reviewing some 20 cases, Dillaha et al. reported success in treatment with Diodoquin in their patient. Diodoquin was likewise helpful in the patient of Bloom and Sobel (JID 24 167 1955) who found cysts of *Giardia lamblia* in the feces. Sulzberger and Baer (YBD 1954 p. 25) were impressed with similarity to infection with *Ca dida albicans* which was present in various cutaneous lesion of Bloom and Sobel's case Sulfamethazine succeeded in an atypical, bullous case in a boy without gastrointestinal symptoms studied by van der Meulen (BJD 67: 16, 1955) The eruption was psoriasiform in the case of Hodgson-Jones (BJD 67: 222, 1955)

THE UNCOMMON FIGURATE ERYTHEMAS

Erythema Annulare Centrifugum is an erythema multiforme-like disease, characterized by a centrifugally progressive, annular erythematous eruption (Darier AnndeD 6: 57 1917) The eruption begins with discrete papules, which enlarge so that within a few hours circular red areas are present. The thickened, firm pinkish border may be elevated and even somewhat scaly Evolution and confluence of lesions result in the production of festooned, ar cuate or polycyclic figures which tend to clear centrally and to become con centrically banded. They may cover large areas of the trunk, rarely involving the face. Their appearance changes quite rapidly a design breaks up dis-



Fig. 1064.—Erythema annulare centrifugum. (Hopkins: ADS 41, 162, 1938.)

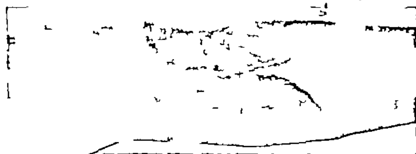


Fig. 1065.—Erythema perstans, involving the leg. (Dr W Herbert Brown.)

appears and is replaced with new elements of the same type. Symptoms are mild and variable, but generally do not exceed moderate itching The eruption tends to involute of itself, reappear rapidly and again evanesce, and so is manifested as a chronic relapsing disease. I have seen cases associated with vesicular tinea of the feet, and believe that the disease is sometimes a der matophytid. This was true of the patient of Jillson and Hoekelman (ADS 66: 738 1952) Louste and Rabut (BsocfrançD 41 750 1934) believed that the disease occasionally turns out to be dermatitis herpetiformis. Sulfonamides lieved the recurrences in the patient of Epstein (ADS 59 488 1949) Tapner (DWehn 130 1334 1954) was impressed with the prompt effectiveness penicillin as well as the latitude of Darier s description, which was ample he inclusion of an assortment of manifestations.

See Graham and Throne (ADS 22, 777, 1930) 6 cases all beginning during, and some in hot weather; Butler (ADS 28 111 1933) case and review; Touraine and (AnndeD 5 361, 1934) differentiation from II. chronica migrans of Lipschütz, wherein

occurs a single ring without vesiculation, desquamation or itching; Wise, also Niles (ADS 33 917, 1936) cases, Lewis (ADS 40 1067 1939), case; Hopkins (ADS 40: 162, 1939) case Wernsdorfer (AfDuS 182 41, 1941) 2 cases; Winkler (ZtschrHInG 7 373, 1949) case van Steenbergen (Dermatologica 99 1, 3, 1949) 2 cases, Montgomery (ADS 60: 444, 1949) case recurrent for 8 year ; Stillians (ADS 67: 590 1953) case associated with metastatic carcinoma in peritoneum Ellis and Friedman (ADS 70 460 1954) histologic differential diagnosis.

Erythema Chronicum Migrans.—Lipschütz (AfDuS 118: 349 1913) used this title in describing an afebrile erythema which began as a small ring that slowly enlarged. The border half an inch wide and slightly edematous, was pinkish red. It progressed at the periphery healed in the interior and left the center slightly pigmented. Such lesions may not be solitary As originally described they are not vesicular or scaling, a difference from erythema annulare centrifugum, which undergoes speedier evolution. Association with meningiti wa originally noted by Hellerström (ActaD-V 2: 315, 1930) who (South MJ 43: 330 1950) described the disease as the result of tick bite, followed by erythema and subsequent cerebrospinal meningeal symptoms which subside in some 3 months. He found organisms in the lesions resembling spirochetes and obtained prompt cure with penicillin. Resemblance of the few cases I have seen to low-grade erysipelas led me to give penicillin, which was curative.



Fig 1056.—Erythema gyratum repens. (Gammel ADS 66 494, 1952.)

See Afzelius (ActaD-V 2 120 1921) Bruhns (AfDuS 138 109 19 1); Lipschütz (AfDuS 144 365, 1923) case nd review of 5 thers Askani (DWchn 101 126, 1940) etiology Sprecher (MinervaM 29 256 1938) case following bite Bruder (DWchn 121 337 1950) following arthropod bite.

Erythema Perstans is a title applicable to chronic disorders characterized by the occurrence of variously sized and shaped, purplish, macular lesions on the extremities. Occasionally the e are present appreciable igns of inflammation and the symptomatology would indicate a relat onship to frostbite pernio erythema multiforme erythema nodosum o nodular vasculitis

Erythema Gyratum Perstans.—Two cases, a brother and sister were e hibited by Colcott Fox in 1881 according to Klabe (BJD 58: 111 1946) The lesions began with small papules accompanied by extreme irritation and extended centrifugally so that within a few hours there were rythematous rings s rrounding a disc of slightly pigmented but otherwise normal kin. On the inner border of each narrow red, advancing ring was ragged cuticular fringe a scaly collarette such as occurs in pityriasis rosea. As the rings enlarged they met and fused with other similar rings, thus resulting in large festooned or gyrate lesions. The shoulders thighs and b ttocks were most markedl affected. S mmetry was well marked. There were exacerbations at irregular intervals. Klaber reviewed

the presumably distinctive features of marked pruritus wide extension of the disease, prolonged duration, onset in early years, familial incidence the vesicular border and collarette desquamation; but no feature seemed entirely reliable diagnostically and typical cases are rare.

Erythema Figuratum Perstans.—A chronic type of erythema which was characterized by the occurrence of persistent erythematous patches, which assume annular marginate, and gyrate forms, differing essentially from other varieties of erythema, was described by Wende (JCutD 24: 241 1906; J 51 1936, 1908) The trunk is the site of predilection for the development of the lesions, which usually are at first red in color but later assume

SOME OF THE RARE ERYTHEMAS (Gammel: ADS 66: 494, 1933)

TYPE	AUTHOR	COMMENT
E. exudativum multiforme	Hebra, 1834	Was known as E. marginatum papulatum, tuberculatum (Willan) gyratum (Fuchs) annulatum, circinatum, centrifugum (Biett) E. iris (Rayer) herpes iris and herpes circinatus (Willan)
E. gyratum perstans	Fox, 1881	Scattered papules, blanched under pressure spread rapidly peripherally in to large gyrate lesions, lasted decades
E. perstans pseudoleprosum	Araing 1809	Brownish livid patches with elevated borders on lower limbs, responded to chrysarobin
E. exudativum perstans	Sachs, 1901	Lenticular papules, formed rings of up to 10 cm. diameter in 8 to 10 days, borders hard, center depressed lasted days, weeks, months
Erythème annulaire	Danlos, 1901	Diabetic patient with annular erythematous lesions, rings up to 2 cm. size, 3 weeks duration; Hallopeau diagnosed urticaria
E. marginatum perstans	Pin y 1903	Pinkish red elevated lesions, linear, curved or segmentary on covered parts of body some pigmentation and scaling
E. circinatum recidivans	Bloch 1907	27 years duration; large symmetrical, circinate pat hes, each consisti g of groups of circinat lesions
E. figuratum perstans	Wend 1906-1908	Circinate lesions, rapidly spreading to rings up t 15 cm. diameter; outer edges smooth, inner edges scaly 4 to 16 years
E. chronicum migrans (perstitens) (dermatitis m grans Afzelius, 1908)	Lipschütz, 1914	One or two giant lesions with diameter of up to 50 cm.; virus infection? Allergic reaction to wood tick bite?
E. annulare centrifugum	Darier 1916	Polycyclic, annula or gyrat arrangement keloid l ke consistency o scales, crusts or vesicles asymptomatic
E. microgyratum	Strempel, 1922	Cinnabar lesions 5 to 30 mm. in diameter became confluent, lasted several months; patient had ulcerative gingivitis
E. simplex gyratum	Jadassohn, 1928	No exudative phase or cyclic course, irregular localization annular macules, no discomfort
E. gyratum migrans	Gammel, 1918	Widespread gyrate bands of erythema with linear desquamation, configuration resembling the grain of wood

purplish or violaceous hue. They finally disappear leavi g a brownish, pigmented patch which may be uniform, but often is stippled or reticulated. The d ration of the lesion varies, but many persist for weeks or even months before undergoing involution.

Histologically the striking feature of the section noted by Wise (InterstateMJ 4 747, 1917) was the paucity of the pathological alterations manifested in what ppeared to be an ctively evoluting, distinctly indurated lesion The induration evidently was the result of the i tense edema of the connective tissue f the kin. The changes differed little from those iti g in ordinary types of multiform rythema in its maculopapular stage. See Meek (JCutD 35: 635, 1917) 2 cases; Gilmour (ADS 1: 349 1920) case; Kindle (BJD 61: 107 1919) case unresponsive to treatment.

Erythema Gyratum Repens was the title chosen by Gammel (ADS 66: 494, 1952) as appropriate for his remarkable case affecting a woman with cancer of the breast who showed a generalized eruption consisting of peculiarly gyrate and irregular wavy bands, the erythema of which moved constantly at a rate of about 1 cm. per day and was followed by linear desquamation of the areas undergoing healing. The dermatosis disappeared within a few weeks after removal of the breast cancer and the regionally involved lymph nodes. See Skin manifestations associated with internal cancer (p. 1319)

ERYTHEMA NODOSUM

Symptoms.—Erythema nodosum is a dermatologic syndrome characterized by the eruption of a few or several painful nodules which persist for 2 or 3 weeks and then disappear spontaneously. The appearance of the lesions is usually preceded by a slight rise of temperature, general malaise and rheumatoid pains. Nodules develop quite rapidly and reach their full size in from 6 to 24 hours. They are circular or oval in outline, tense, shiny and bright red at first, and commonly involve the extensor surfaces of the legs, their long axes parallel with those of the affected limbs. They range from 2 to 6 cm in diameter and are occasionally raised above the surface of the surrounding skin. They may be firm or elastic, or soft in consistency, and are deeply embedded in the skin. Their outline is fairly well defined but not sharp. They are painful and tender on pressure. After attaining their full

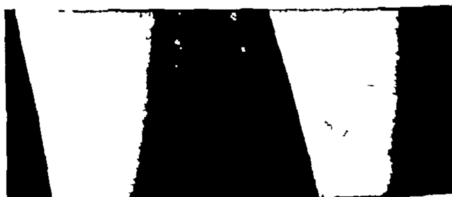


Fig. 1057.—Erythema nodosum, affecting the shins.

size they gradually subside, changing in color from bright red to red, then dark red and purplish, and finally disappear, leaving greenish or brownish stains which persist for several days. During the period of regression the lesions often become soft and fluctuant and may be mistaken for abscesses. Suppuration of the nodes does occasionally occur but is rare. As a rule the mucous surfaces are not affected. In number the lesions range from 2 or 4 to 20 or more. They are generally roughly symmetric in location. Nodules may appear in crops, so that an attack may be prolonged over several weeks.

Etiology.—The disease occurs most frequently between the first and third decades, and during the spring and fall seasons. The lesions can be caused by several different agents: drugs such as iodides, bromides, sulfonamides, penicillin and antipyrine; infections, such as tuberculous, streptococcic and meningococcic; and miscellaneous diseases including syphilis, leprosy, filariasis, lymphopathia venerea, erythema multiforme, trichophytosis, chancroid, influenza, ulcerative colitis, rheumatic heart disease and coccidioidomycosis (Spink, AIntM 59: 65, 1937; Poppel and Melamed, NEngJM 227: 325, 194*; Crawley, BMJ 2: 1362, 1950). Except in the regions where coccidioidal disease is endemic, tuberculosis is a common cause.

Lesions as of erythema nodosum occur in coccidioidal infection (q.v.), appearing as the preliminary illness of coccidiomycosis, due to inhalation of the chlamydospores resulting in infection of the respiratory tract with symptomatic erythema nodosum in many

cases, a disease from which the great majority of patients recover completely though it may progress to coccidioidal granuloma; in these cases the coccidiodin cutaneous test is strongly positive.

In poliomyelitis, years after paralysis, reddish-purple nodules may appear in the lower part of the legs, often in the posterior tissues in association with hyperhidrosis and dependent cyanosis (Telford and Stopford: BMJ 2: 770, 1933) Such cases, I have found in confirmation of the report of Stenort (abs J 128 9?6, 1945) are responsive to vasodilator medication. Cortisone is helpful, too.

The syndrome occurred in cases of bacillary dysentery as reported by Keizer (abs J 113: 1266, 1939)

Relationship with heumatic fever was denied by Kell (AnnIntM 10: 1686, 1937) and by Doxiadis (BMJ 2: 844, 1949) See Rheumatic nodules.

Erythema nodosum may be thought of as a nonspecific allergic syndrome (Edit J 113: 147 1939) A known respiratory infection antedated erythema nodosum in 126 of 155 cases studied by Favour and Sosman (AIntM 80: 435, 1947) Half of their throat cultures revealed beta hemolytic streptococci; migratory polyarthritis was part of the picture in four-fifths of the adults and in one-third of the children, but rheumatic heart disease was a rare sequel. Collis (QuartJMed 1: 141, 1932) believed that the syndrome may be brought about by more than one organism or allergen; in London this may be streptococcic, in Scandinavia, tuberculous. Ernberg (FinskläkSällskHandl 74: 164, 1932), of Finland, was convinced that all cases, or nearly all, result from infection with *M. tuberculosis*.

Moon and Strauss (ADS 26: 78, 1932) investigating 3 cases, were able to recover an organism of the genus *Corynebacterium* in each instance, and cultures from the inflamed periapical tissue of infected teeth revealed the same organism. The case of Elmell (BMJ 1: 974, 1936) associated with purulent adenitis, was relieved by incision and drainage f that, and by removal of dental foci. Coburn and Moore (JClinInv 15: 509 1936) injected the nucleoprotein of a hemolytic streptococcus intradermally into the arm of a girl 11 years old; this provoked recrudescence of the lesions on the legs. Spink (1937) found that streptococcus nucleoprotein put into the skin caused marked reaction in 8 of 10 cases, with the development of new lesions in 2. He expressed the opinion I hold in stating that erythema nodosum is a reaction that can be evoked by various bacterial, toxic and chemical agents. Repeated attacks associated with streptococcic infections of the throat were observed by Forman (BJD 48: 122, 1936)

Tuberculous infection and allergy are frequently the cause, though less often in the United States than in the Scandinavian countries and Europe as judged by the literature. Weber (BJChildDis 31: 119 1934) belie ed that the disorder is generally, but not invariably a manifestation of tuberculous bacillemia. An acute epidemic was described by Ledoux (RevMéd 140: 32 1923); Wallgren (ActaTuberc 3: 353, 1927) reported an epidemic in a school; and Brandon et al. (CanadPHJ 29: 533, 1938) attributed 14 cases in a school of 173 boys to tuberculous sensitivity Six patients of Thompson (BMJ 1: 159 1939) had tuberculous cervical adenitis. Magnusson (BeitrKlinTuberk 63: 657 1928) called attention to the fairly frequent association with tuberculosis in his clinic. Gobel and Schuchardt (ZtschrfTuberk 63: 260 1934) stressed the tuberculous factor in th etiology of a high proportion of the cases. Roines (ActaD-V 17: Suppl 3, 1936) insisted that the overwhelming majority of cases seen in Oslo are tuberculous in origin. Landorf (RévfrançPédiat 1935 p. 157) recorded positive reactions to tuberculin in 97% of 650 cases. Erythema nodosum followed tuberculin tests in 4 children, as reported by Bindschedler (BaselPéd 34: 545, 1936) The 9 cases reported by Gray (BMJ 2: 286, 1945) were all associated with tuberculosis, and all reacted positively to tuberculin. Bilateral hilar lymph node enlargement was present in 6 cases of Dunner and Harmon (BMJ 2: 1078, 1952) In a tuberculous individual, an intercurrent illness, such as measles, may precipitate erythema nodosum (Debré et al.: RévfrançPédiat 14: 433, 1938)

The presence of erythema nodosum necessitates roentgenologic examination of the chest, for some cases at least are associated with activation of pulmonary tuberculosis (Deaner BMJ 1 357 1935) Typical, idiopathic cases are always due to tuberculous bacteremia in both the child and the adult, according to Ramel (BaselfrançD 1938, p 1138) While the disease usually resolves spontaneously it may progress into fatal tuberculosis, even with meningitis. Erythema nodosum in childhood is followed by pulmonary tuberculosis less often than in adults (Ingebrightsen abs J 114: 1972, 1940) yet epidemics of erythema nodosum have indeed been traced to a tuberculous source of infection.

Pathology—The epidermis is little altered. The vessels of the papillary plexus are dilated, with extravasation of both white and red cells. In some capillaries leukocytes are packed so closely as to resemble white thrombi. There is widespread infiltration throughout the dermis. Late in the disease, disintegration of extravasated red cells results in more or less pigmentation.

Histologic studies were given by Miescher (ActaD-V 27: 447 1947) who could not by microscopy distinguish tuberculous from nontuberculous cases. He thought characteristic the collections of closely packed small histiocytes, elongated or even spindle-shaped, often arranged in radial fashion sometimes giving the appearance of a central syncytium. Some giant cells resulted from their fusion. See Winer (ADS 63 347 1951) on histologic distinction from erythema induratum, panniculitis and periarteritis nodosa.

Bacteriologic studies of nodules from 28 children who gave positive tuberculin reactions were made by Wallgren and Gnospelius (ActaMScand 103 341, 1940) Only 1 of the 28 yielded a positive guinea pig inoculation.

The spinal fluid pressure was found increased in 10 cases, but no other change was present to account for the headache and anorexia in the patients of v Moritz (Monatschr Kinderh 67: 255, 1936)

Diagnosis.—The multiplicity of the lesions, their symmetry their tenderness, and the attendant constitutional symptoms should serve to differentiate them from gummas bruises and staphylococcic abscesses. From nodules of sporotrichosis they are to be recognized by their bilateral distribution and the absence of a chancre. In erythema induratum the sites of predilection are the calves the disease is of slow development the lesions are dark red from the beginning and sometimes ulcerate and the histologic structure is that of tuberculosis.

Prognosis is favorable complete recovery usually taking place within a month Determination of the cause is of course pertinent to prognostication. In rheumatic cases, the heart should be completely examined at intervals in order to detect pericardial or endocardial involvement, if this should occur

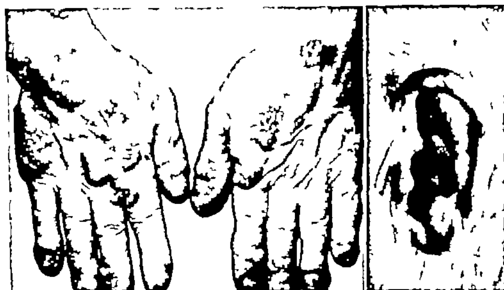
Treatment.—The patient should abstain from exercise and confinement to bed is advisable Sodium salicylate 10 grains t i d., is palliative Locally a 10% ichthyol ointment may do good, or if there is present a feeling of tenseness a cool, soothing astringent, such as aluminum acetate compresses may be applied. Treatment varies with the disease which underlies the syndrome Cortisone in full dosage has been reported as promptly curative by Ureles and Kalmansohn (NEngJM 245 30 1951) and Schneierson (J 150 685 1952) but the drug is known to be dangerous in the presence of tuberculosis.

See Klander (ADS 35 1067 1937), review; Wallgren (Lancet 1 359 1938 AmDisChild 55 897, 1938) nonspecificity of syndrome, which may nevertheless sometimes represent rheumatic fever; Wallgren (ADisChild 14: 271, 1939) renal lesions and capillary fragility; Greene and Perry (AmJOphth 22 389 1939) conjunctival nodules in erythema nodosum; Simon (abs J 116: 1633 1941) response to sulfanilamide; Paul and Pohle (Radiol 37 [illegible] 1941), chest film abnormalities in 12 of 26 cases; Lofgren (Erythema Nodosum, Norstedt, Stockholm, 1946) etiology and pathogenesis in 185 adult cases 104 tuberculous, 30 streptococcic, others various quoted in bra a standard description Parker et al. (VaMedMonth 74 317 1947) benefit with Pyribenzamine Ladit (J 144 1562, 1950) sulfonamide sensitivity Wasserman and Yules (AmPract 2 772, 1951), 50 cases, including some due to dental infection and ulcerative colitis, Fry (BMJ 1 579 1951) 3 cases, all tuberculous in 1 family Beerman (AmJMedSci 223 433, 1952) review and bibliography, Olsen (abs J 167 279 1955) biopsy of nonpalpable cervical lymph nodes in 9 cases showed tuberculosis in 4 and sarcoid in 4.

ERYTHEMA ELEVATUM DIUTINUM

Erythema elevatum diutinum was the name applied to a persistent nodular eruption by Crocker and Williams (BJD 6 1 33 148 335, 1894) Similar symmetric, purplish, congestive lesions were seen also in elderly gouty men. The lesions appeared to be inflammatory fibroses analogous to subcutaneous rheumatic nodules. Analyzing previous reports, Ketron (ADS 50 363, 1944) illustrated a rheumatic woman whose photographs are reminiscent of eruptive xanthoma affecting buttocks, extensor regions of elbows and dorsa of hands but fat was not found in sections of the irregular reddish or purplish plaques, elements of which sometimes healed spontaneously without scar Ketron described a toxic hyalin about the blood vessels. The patient of Weidman and Besancon (ADS 20 593 1929) was also rheumatic. The possible relationship to granuloma annulare was discussed by Templeton (BJD 40 103 1928) This was denied by Combes et al. (ADS 57: 219 1948) who summarized the features of erythema elevatum diutinum as follows occurrence in the 40- to 60-year age group especially in males distribution roughly symmetric and bilateral duration persistent histologic structure an acute process with polymorphonuclear leukocytes and eosinophils but without necrosis individual

lesions not discrete but flat, raised and red, without central clearing location on hands and feet, less often on wrists, ankles, neck, knees and buttocks unresponsiveness to x ray therapy; ulceration sometimes occurring and if so productive of deeply pigmented scars.



Figs. 1058 and 1059 —Erythema elevatum diutinum. (Combes et al.: ADS 57 219 1948.)



Fig. 1060.—Erythema elevatum diutinum, lesions of knees. (Combes, Dehrman and Saperstein ADS 57 219 1948.)

The abundant perivascular leukocytosis and the toxic hyaline degeneration of the fibrous tissue about the capillaries seen by Weiss et al. (ADS 58 710 1948) were interpreted as representative of toxic dermal periarteritis

and peritelangiitis, in confirmation of the observations of Weidman and Besancon (1929) While the histologic changes are characteristic they are not pathognomonic, stated Haber (BJD 67 121 1955)

Treatment of a specific sort has not as yet been designed, for the cause is entirely obscure If the cutaneous lesions represent basically a kind of peripheral vascular disease possibly related to periarteritis nodosa, cortisone should be helpful I believed it to be so in 2 patients seen in 1954

See Combes and Bluefarb (ADS 42 441, 1940); Bagman et al. (ADS 45: 314, 1942) Tulipan (ADS 57: 841, 1948); Cohen (BJD 60 421, 1948); Haber and Russell (BJD 62: 446, 1950)

GRANULOMA ANNULARE

Symptoms.—Granuloma annulare is a chronic inflammatory dermatosis characterized by grayish white or pinkish, flat topped, intracutaneous nodules which spread centrifugally and form circular and arcuate lesions. The disorder usually develops slowly the first clinical manifestation being a localized, deep-seated infiltration of the skin without appreciable reddening Ringlike lesions result from central involution and peripheral extension. An annular lesion is often beaded. Mature lesions are slightly raised and of a firm or doughy consistency The sites of predilection are the backs of the hands. Wrists feet ankles, neck, knees and buttocks may be affected. Lesions are usually but not always, few in number and range from 0.5 to 5 0 cm. in diameter On superficial examination the central portion of the rings appears normal, but atrophic changes may be noted.

Atypical forms were described by Vissian (AnndeD 8 363, 1948) nodules not annular giant forms punctate forms forms resembling tuberculoid leprosy keloid lichen obtusus or lichen planus forms with hypodermal involvement and necrotic evolution and forms of unusual location, such as palmar or nuchal Large circinate lesions as well as lesions of the usual kind were seen by Goodman and Ketron (ADS 33 473 1936) who commented that histologically the inflammation was notable for the absence of polymorphonuclear leukocytes Subcutaneous lesions do occur rarely as noted by Grauer (ADS 30 785 1934) in describing a 2-year-old child with lesions of the scalp as well as of the wrist and shin. Tuberculo-ulcerative or gummatous cases are rare but 5 such were described by Civatte (AnndeD 79 387 1952) The lumpy lesions on the backs of the hands and fingers of a young man seen by Calnan (BJD 66 254, 1954) sometimes discharged thick creamy or glairy material Identical twin girls aged 9 years, were both affected, noted Cohen and Schiff (ADS 67 117 1953)

Etiology—The cause is unknown. It is a comparatively rare disorder It occurs most frequently in children, and develops oftenest during the summer months. Michael (ADS 29 189 1934) with a report of 8 cases, concluded that there is no evidence favoring the hypothesis of tuberculous origin.

Pathology—In the subpapillary region there is widespread cellular infiltration with lymphocytes polynuclears, epithelioid cells and spindle cells of the connective tissue type In old lesions necrosis occurs in the center of the infiltrated areas While similarity to necrobiosis lipoidica was noted by Ellis (ADS 43 822, 1941) Combes and Bluefarb (ADS 42 441, 1940) and Laymon and Fisher (ADS 59 150 1949) distinguished the disease clearly from erythema elevatum diutinum and necrobiosis. Mucin was found mainly in foci of altered connective tissue in 24 of 29 cases by Freudenthal (BJD 57 177 1945) confirming the observations of Prunty and Montgomery (ADS 46 394 1942) Histologic similarity to rheumatic nodules was not interpreted as implying etiologic identity by Bowers (BJD 61 247 1949)

Prognosis—The disorder is essentially benign though chronic. The lesions may persist for months or years, and then disappear spontaneously The nodules almost never ulcerate and the patient remains essentially unharmed.

Treatment.—Roentgen therapy is efficient, a few doses of 150 r with filtration being appropriate although lesions are likely to recur Freezing with solid carbon dioxide will generally cause a nodule to disappear Sulfonamides (Ingels ADS 43 877 1941) and penicillin have apparently cured some cases but are not dependable therapeutic agents. O'Farrell (ADS 50 323 1944) saw 2 cases clear after intercurrent measles. Spontaneous regression after biopsy is not unusual (Gaté BsocfrançD 46: 926 1939) Radial incisions, shallow yet penetrating the dermis, may be followed by involution (Robinson



Fig. 1061—Granuloma annulare. (Dr E J Angle)





Fig. 1062.—Granuloma annulare. (Dr Ise e R. Pels.)

Fig. 1063.—Granuloma annulare. In the subpapillary layer is a mass with borders composed of spindle cells. I the center necrosis has taken place. Polymorphonuclear cells nd lymphocytes are present. (Dr Stuart Way)

ADS 67: 320 1953) Resolution followed intercurrent measles, Dwyer told me (Kansas City Dermat. Soc., Mar 1956) and Grindon stated that, having seen this himself he injected measles immune serum into 2 patients with surprising success. Vitamin E (alpha tocopherol) given to 13 patients seemed to result in cures in 9 and improvement in all but 1 reported Cochrane (BJD 62 316 1950) Massive doses of vitamin E, ranging from 0.3 to 1.25 Gm. daily combined with pantothenic acid derivatives, constitute a safe and effectual therapeutic program, according to Welsh (ADS 70: 468, 1954) Cal

ciferol, often helpful in sarcoid to which granuloma annulare bears some superficial resemblance made the latter disease worse reported Hall (ADS 61 145 1950) an observation confirmed by Sawicky and Kanof (ADS 64 58 1951)

See Fox (BJD 7 91 1895; 8 15, 1896) ringed eruption on the fingers Galloway (BJD 11 221, 1899) lichen annularis, a ringed eruption of the extremities, Radcliffe-Crocker (BJD 14 1, 217 1902) granuloma annulare; Little (BJD 20: 213, 248, 317, 1908) review Beneck (ADS 38: 280 1938) relation t sarcoid Boldt (AfDuS 1 9 603, 1940) description nd etiology

ECZEMATOID DERMATOSES OF UNDETERMINED CAUSE

INFANTILE DERMATITIS

Dermatitis In Infants is of heterogeneous causation as it is in adults Friction and chafing are commonplace Defatting and oversoaping often irritate Wool and laundry starch are more likely to cause mechanical damage than allergic phenomena Wool dermatitis in children affects especially the neck, ankles, wrists, dorsa of the hands and the arms and legs in areas of maximum contact and is worse in the winter (Hill NEngJM 245 407 1951)

Contact dermatitis affects infants as it does older individuals, the likely irritants being soap baby oil fabric finish medicinal substances applied to the skin, garments and toilet articles of those who handle the baby (nail lacquer for example) the textiles of the environment (carpets and coverings of furniture) the various things which may be on the floor (wax, spilled detergents and antiseptics) and chemicals reaching the infant s buttocks by way of diapers or toilet seat Contactants are the usual cause of dermatitis in infants, according to Tachau (ActaD V 19 587 20 1 232 1939)

Bacterial especially staphylococcic and streptococcic and mycotic especially monilial infection may occur as primary diseases or as complications of traumatic or chemical dermatitis. The monilial type of infantile dermatitis is characterized by the appearance of circular and oval plaques of yellow red, minutely vesicular disease marginated and with predilection for the napkin area Infection primarily of internal tissues, such as the upper respiratory tract may spread onto or inoculate the skin, producing such diseases as infectious eczematoid dermatitis or even cutaneous diphtheria. Impetigo and infectious eczematoid dermatitis of the newborn (q v) represent streptococcic and staphylococcic parasitism Seborrheic dermatitis may produce infantile dermatitis of the scalp and may spread to other parts of the body

Disorders of nutrition and metabolism affect the skin of infants, who are subject perhaps to a greater degree than adults to undernourishment overnourishment nutritional imbalance and troubles with vitamins, including overdosage thereof The role of allergy to foods requires further discussion. One infantile eruption clearly dependent on foods and seen not infrequently is acneiform, with or without actual pustulation and responds promptly to diminution of lipid rich substances and oily vitamin concentrates One instructs the mother to pour the cream off the milk and diminish the intake of orange juice

Scurf scalp in inf nt may be divided into 3 types, according to Gordon (BMJ 1 352 1940) (1) milk crust d e to lack of soap and water disi clin tion of mothers to rub the scalp hard o e the fontanelle nd application of oils; ( ) true dandruff infection ac red from the mother; (3) mixed, compri ing both of the others When a child ha d druff and gets derm titis d e to atopy o contact the scal g disease of the scalp may pread to complicate the whole

Afte elim n ting diagnostically and therapeutically the d rmatitides enumerated above there rema ns mo g infants a common, well-defined entity disma ing to patie ts, parents and physic ans, ent tled infantile eczema. The name eczema, elsewhere i this volume d fined as d rmat tis of unknown cause is ppropriate here. The difficulties in distinguishing in the early cases between atopic, seborrheic and cont ct dermatitis were discussed by Glase (J 137 5?7 1948), who comme ted on the f ct that one can not predict which ch ld w ll outgrow the d sease He thought th i cidence consid erably less in breast fed babies than in those artificially fed; I doubt that this is so.

ATOPIC DERMATITIS

Definition.— Atopic is an adjective applied by Coca and Sulzberger (Sulzberger Dermatologic Allergy Thomas, 1940 p 158 ff.) to designate a *type of sensitization characterized by a familial tendency to the development* of certain forms of disease principally hay fever asthma, infantile dermatitis, and a chronic relapsing rebellious lichenifying dermatitis which differs distinctively as a clinical entity from other dermatoses. In atopy one observes in a family the common occurrence of urticarial reactions to skin tests, demonstrable reagins, and the above-listed disease forms. Atopic individuals in an incidence significantly higher than other individuals evince these particular and peculiar abnormal forms of allergy which differ from ordinary acquired sensitivity and from intolerance of contactants. Atopic





Fig. 1064.—Atopic dermatitis in an infant. (Dr J Lamar Calloway)
Fig. 1065.—Atopic dermatitis in young adult. (Dr Clyde L. Cummer)

dermatitis is to be recognized as the childhood and adult manifestation of infantile eczema which is itself atopic rather than the precursor of atopy (Hill and Sulzberger ADS 32 451 1935) Hay fever and asthma usually precede but may accompany or follow atopic dermatitis.

See Coca (J 103 1275, 1934) familial allergy; Sulzberger (NEngJM 218 330, 1938), forms of dermatologic allergy; Wise (JMichSMS 36 270, 1937) Caesena in 1844 recognized relation of "Besnier" prurigo with hay fever and asthma; distinction from lichen chronicus simplex; Casper (AfKinderh 115 98, 1938) 210 cases of simultaneous asthma and eczema. Urbach (APediat 58 481, 1941), topy and anaphylaxis; Epstein (AnAllergy 2 247 1944) review Ratner et al (AmJDisChild 82 666, 1951) "allergic dermal respiratory syndrome, 750 cases reviewed, *eczema generally manifest during first year and asthma prior to age 5,* usually by age 4; O'Leary (SouthMJ 46 47 1953) inadequacies of etiologic concepts; various manifestations of the syndrome may be present in various degrees and are not the cause

Infantile Eczema.—Itching is the initial manifestation. The infant scratches with every means at its command There successively develop erythema abrasion, oozing crusting and secondary infection. The flush areas of the cheeks are the sites of predilection, and the forehead, ears, scalp extensor

surfaces of forearms and arms and legs and thighs are likewise often involved. This description fits such cases as are said usually to be due to food allergy and are called 'atopic (see p 861) While the onset may be early in life, the immediate newborn period is notably free from manifestations (Ratner J 111 2345 1938) The average age at onset was 5 months in the extensive series of Edgren (abs J 137 164, 1948) who determined that dermatitis faded out between the ages of 15 months and 3.5 years, averaging 2 years, but recurred in one fourth of the patients, and was succeeded by atopic eczema in 18% of the patients who were followed for from 17 to 38 years. The incidence was equal in breast fed and bottle-fed babies.





Fig. 1066.—Impetiginized infantile eczema. (Dr Robert N. Andrade.)
Fig. 1067.—Impetiginized atopic dermatitis. (Dr Clyd L. Cummer)

Dermatitis in a baby cannot long persist without becoming secondarily infected with parasites capable of arousing sensitization just as occurs in adults. In any case in which cure is not promptly forthcoming the disease is likely to become chronic and persistent, rebellious to treatment, and prone to undergo relapses and recurrences. Extension of dermatitis from the cheeks may come to involve progressively larger areas the head, arms, legs, even the entire body Some pitiable patients may be universally exudative exhibiting general lymphadenopathy and a white blood cell count so high as to suggest leukemia although it is actually inflammatory (Larkin et al. J Pediat 24 442 1944) while serum proteins are depleted and red cells so reduced that transfusions are essential Milder disease is fortunately more common, and there is a tendency upon which one should not rely too confidently for dermatitis to fade as the child grows older A long time study by Vowles et al. (BJD 67 53 1955) clarified the natural history and prognosis. Of 84 cases, 6 died of some infection during infancy One-fourth cleared by the time they

reached 3 years of age. Eczema was still present at age 13 in 65% and many still suffered at age 20 Asthma, recurrent bronchitis or seasonal rhinorrhea was present in 73% of the patients 50% had asthma alone.

Multiple abscesses, bronchopneumonia and gastroenteritis may terminate the case, mortality being estimated at from 4 to 14% (Glaser and Edwards: AmJDisChild 60 526 1940) Of 10 deaths reported by Schwartz (JPediat 4 172, 1934) 4 were septicemic, 2 bronchopneumonic, and 2 due to intestinal intoxication. Epstein (JPediat 26: 541, 1945) surveyed 100 hospitalized cases, among which all the deaths occurred in infants under 2 years of age. Coal tar he pointed out, may be toxic. The toxicity of boric acid is noted under Dermatitis medicamentosa (see p 175) Sudden death proving inexplicable even after autopsy has been known to occur in cases of infantile eczema. Such







Figs. 1068-1070.—Infantil eczema

tragedies occur especially during the first year especially in fat babies, and especially during the first few days of hospitalization when the infant is away from the mother (Davies BJD 2 182, 1940) The peak incidence of Davies series was in March. Fulminant and overwhelming infection is the probable explanation. The thymicolymphatic hypothesis has by now been laid to rest.

Etiology —Dermatitis in infancy like dermatitis in adults, is hardly to be ascribed to one agency in all cases (Silvers and Coe: JPediat 16 160 1940) The dermatologist sees so many infants whose diets have been juggled as the sole effort toward curing what was in fact scabies, contact dermatitis, or coccic parasitism, that he tends to discount food intolerance almost as emphatically as the average pediatrician has stressed it In some cases, how ever real food allergy exists. Milk is the commonest single offender wrote Bain (SouthMJ 34: 863 1941) Evaluating elimination diets in 198 cases, Birt (CanadMAJ 42 520 1940, reported eggs worst, then tomato orange juice milk, fish, oatmeal and cod liver oil.

The actual clinical trial of the food, a procedure subject to ready misinterpretation because of the erratic and unpredictable course of the disease, is the most dependable method of identifying intolerance (Hill J 140 189

1949) If a mother tells me that feeding her infant a particular nutrient results *each time in conspicuous ill effects, I believe her* I advise her to keep her observation of the child alert to such occurrences. This accommodates her preoccupation with an aspect of the treatment which is of little interest to me because my patients almost always do well nowadays without regard to diet, provided that it is adequate. Food allergy sometimes is significant.

Skin tests yield falsely positive and falsel negative reactio more often than the yield useful information so that candid allergists tell me they employ skin tests to satisfy a demand rather than to enable themselves to aid the patient. Positive reaction to egg white is obtained in a high proportion of all cases, even in some patients who have never been exposed to the substance and perhaps carry reactivity by passi e transfer from the mother (Pčhu and Woringer ActaPaediat 14: 36 1933) The presence of a positive reaction is not necessarily correlated with intolerance evinced by exacerbation when the food is ingested. Lack of confidence in skin tests has been voiced by ma y in luding Levin (JMichSMS 36: 645 1937) and Bowen and Bloom (SouthMJ 42: 492, 1949) Routine scratch and intradermal testing is entirely inadequate, unreliable and misleading in these cases, according to Osborne and Walker (ADS 38: 511, 1938) a view with which I concur The elimination of a food may improve the patient when the skin test i negative (Hill JPediat 12: 725 1938) I do not perform skin tests and without hesitation dismiss them as being without practical value.

Urbach (Nutrition and Metabolism, Grune & Stratton, 1946) described (1) the o er nourished fat child, who improves when the milk is cut down; (2) the d strophic marasmic, enteritic infant with dry eczema who improves when the diet is improved; (3) the exudative patients with crusts on the scalp and face who go on to have atopic dermatitis and are allergic to milk and (4) cases of unknown etiology which are not helped by diet changes. Urbach sai l, with commendable candor again and again fail re ha rewarded my sincerest efforts to help these children. Foerster (JOklaMA 30: 60 1937) divided the cases into seborrheic dermatitis, infectious dermatitis, mycosis, and contact dermatitis, and he reserved atopic dermatitis for the remainde This same grouping appealed to Hill (NEngJM 17 690 1937) Foerste found goat s milk well to erated as rule if cow's milk is not. Soya bean preparations ma fail because of an unsuspected bar.ey content.

Gastric analyses performed in 50 children in the age range from 9 months to 1 years yielded no illuminating information, reported Strickler et al. (ADS 51: 189 1945)

Factors of contac ant mechanical and chemical intolerance and autoinoculated coccic parasitism are usually underestimated in interpreting the cases. Even mild agents which may give negative patch tests may be intolerable when long used on large areas. Wool, corduroy and laundry starch are common sources of irritation. Mild food allergy and severe medicinal contact dermatitis are likely to be combined. Greatest offenders are fabric finish, soap unguents (including baby oil and olive oil) and environmental agents such as mattress stuffing less often the agents are associated with the parents clothing (finish dye) or cosmetics (nail lacquer) or the baby s toys (sponge rubber teddy bears) Human dander may be an important contactant (Simon J 125 350 1944) Ammoniated mercury accounts for a fair quota and tar too concentrated, is an irritant. Most salves smear staphylococci about and enhance their pathogenicity

Wool was stressed as a major etiologic factor by Osborne and Murrey (*ADS 68 619 1953) It may serve as a mechanical provocateur* and a contactant and inhalant allergen. It may explain the winter recurrences and summer remissions which occur in some 75% of the patients. Contacts with wool soap laundry starch and corduroy are especially to be avoided.

Hill (J 111 113, 1938) believed that contactants ga n in importance in etiology as the child grows olde while foods are most important in infancy He stated that the seborrheic type with involvement of the cheeks a d scalp is l kely to respond to dietary treatment. He found that of 126 cases actually sensiti e to milk 104 had their onset before 6 months of age and 52 before 2 months. If sensitivity is to the casein fraction, heating th milk will prove unavailing but intolerance of casein is not so common as intoleranc of lactalbum which is readily altered by boiling If boil ng fail to render the milk tolerable evaporated milk, goat s milk, or a proprietary (S.M.A. hypoallergic milk) may be tried. Hill s failures, he said occurred i sev re generalized cases. Elimination diets are given in deta l by Cobb (AmJDisChild 50 187 1935)

TREATMENT.—My practice on assuming control of a case of infantile eczema is to begin with instructing the parents regarding the general nature

of the disease confessing at the outset lack of understanding of its ultimate explanation. The parents need to know that they may expect prolonged difficulties, in all probability and that a physician is satisfied if the patient attains good palliation. One is unable to offer cure. When the infant is in fairly good condition sleeping well and gaining one is pleased, even if some dermatitis persists. I am at times sadly bedeviled by parents who insist that the last trace of dermatitis be eradicated they do not know when they are well off I hedge the prognosis saying I believe that improvement can be brought about and that the disease often but not always fades considerably by the time the age of 3 years is reached and I advise the parents that flexural eczema, asthma or other troubles may appear during teen age even if the infantile stage of disease disappears apparently entirely The picture may be delineated in a ten minute discussion, without painting it too dark. One must be concerned about the next few hours or days rather than about the next several years, attending to the situation as it is, and expecting ups and downs.

The medication which relieves infantile eczema and which has changed my practice conspicuously in recent years is cortisone. ACTH likewise is often eminently beneficial when modest doses are used over brief intervals, the hazards being recognized (DiGeorge and Nelson JPediat 38 164 1951) I have not seen ill effects from cortisone which I consider a safe drug if given in reasonable dosage, in infants as well as adults. Palliation not cure, is obtained, and for palliation one should be duly grateful One gives the smallest dose over the briefest period of time that yields real benefit (Hill NEngJM 248 1051 1953) This dose for an infant may be 5 mg of hydrocortisone in suspension b.i.d. A child 1 year old may be given half of a 25 mg cortisone tablet 2 or 3 times a day The drug is continued for from 4 to 7 days then discontinued until relapse takes place Sometimes the child relapses within 24 hours sometimes the improvement stands up for a week or more. A sign of overdosage easy to recognize is overexcitability with sleeplessness. Sometimes ACTH works well when cortisone does not. I often give infants 15 units intramuscularly twice a week for a while

One must be earnestly concerned with the adequacy of nutrition. Some infants I see have undergone such dieting that they themselves, rather than offending foods have been almost eliminated. Bivings (JPediat 4 494 1934) claimed to have cured 123 of 157 cases by removing offending foods from the diet I am dubious. While skin tests are unreliable antibodies demonstrable by passive transfer technic may be important guides. A basic diet, consisting of soybean emulsion (Levin JPediat 17 70, 1940), or of foods to which scratch tests are negative may be given. It is supplemented one food at a time at intervals of several days until offending and harmless foods have been distinguished and a full diet has been designed. Cevitamic acid may be substituted for orange juice It is a grave error to allow an eczematous baby to endure malnutrition long If a food actually is intolerable it must be totally avoided Heated goat s milk, rice cane sugar and vitamins and minerals are usually trustworthy (Cline WiscMJ 40: 780 1941) The allergenicity of casein is not altered by boiling it (Hill PaMJ 41: 663 1938) and efforts to hyposensitize an infant are generally disappointing

A baby has to eat He is better off scratching on a full stomach than on an empty one In fact satisfying the appetite may allay pruritus. A small amount of a vitamin concentrate such as Olyvisol suffices to assure adequate vitamin intake if orange juice and cod liver oil are suspect. It is not too difficult to put egg out of the baby s life Some kind of milk must be given. If cow s milk seems intolerable possibly boiling it will make it tolerable or an evaporated milk may prove agreeable or goat s milk may be tried, or a soy bean milk substitute may prove acceptable. I desire the help of a pediatrician and I select as my consultant one who believes in feeding these infants plenty to eat, as I do

Protein replacement may be urgent, so that blood or plasma transfusions may be indicated (Wolpe CalifWM 67 156 1947)

Interesting hypotheses regarding the role of fatty acids in nutrition have led to reports of benefit from feeding lard by such authorities as Hansen et al (AmJDisChild 73: 1, 194) Linseed oil has been given for the purpose of increasing the iodine number of the serum lipid by Hansen (PSExperBiol 30 1195; 31: 161 1933) It was adjudged valueless, even dangerous, by Taub and Zakon (J 105: 1675, 1935) and Epstein and Glick (ADS 35: 427, 1937) See Edit (J 134 606, 1947) and QMN (J 135 396 1947) One may believe that feeding lard, corn oil and other fats is probably of no benefit in any kind of chronic dermatitis (Ginsberg et al: ADS 36 1033, 1937) Flares appeared, however to be associated with high unsaturation of plasma lipids in the patients of Stoesser (JAllergy 13: 448 1942)

I concern myself deeply with control of contactants but pay no immediate attention to inhalants or to the drapes, heating system or house dust of the infant s room. The infant s bath may consist in a tepid tub of aluminum acetate solution, a teaspoonful to the gallon of water putting soap aside completely Petrolatum is substituted for baby oil The mother s hands are not to convey nail lacquer to the infant s skin, and lipstick is untrustworthy The garments of those who handle the baby should be of cotton, uncontaminated with laundry starch. The napkin area in infantile eczema is usually free of disease Diaper services may be recommended, for their cleansing methods are professional and they save a tired mother much labor There was a time when diaper antiseptics were a hazard (see Dermatitis venenata, garment) Clothing should be loose and cool, for warmth incites pruritus. The skin may be intolerant of all oily substances.

Investigations of contact and environmental allergens made possible most of the satisfactory results of Osborne and Walker (1933) Their first attack was the elimination of contact and environmental allergens; this alone cured half of their cases and helped two thirds of the remainder Mineral oil and petrolatum, cornstarch, cotton and water are relatively safe The baby s external environment should be limited to these with the implication that those who handle the infant should be free from cosmetic and toilet articles. Wholesale removal of drapes, carpets furniture and toys I sometimes ordered, usually by physicians who are comparatively amateur in controlling contactants and who neglect to interdict soap.

Control of infection is a major enterprise Baths in $KMnO_4$ 2 or 3 grains to the gallon of tepid water may prove useful. Antibiotics (not penicillin) may be applied topically Terramycin given with the formula may effectuate the elimination of cocci. Penicillin intramuscularly Achromycin by mouth, or other such agents may be lifesaving and should be used when exudation is extensive lymphadenopathy considerable white cell count high or fever persistent. These drugs will generally cure boils, abscesses, bronchopneumonia and that portion of the dermatitis which is bacterial. Controlling the hazard of infection by possible carriers who handle the infant is even more important when the skin is inflamed than when the skin of the infant is normal.

Vaccinia inoculated into an infant with eczema is dangerous and may be fatal. The strictest avoidance of the vaccinia virus is enjoined, although the usual diphtheria tetanus and whooping cough immunizations should *not* be postponed unless the child is severely ill at the time

Topical medication is concerned with avoidance of irritation and control of coccic infection. Tetracycline or hydrocortisone ointment has supplanted the traditional tar in my practice The prevention of scratching is highly desirable. An extreme case requires restraint, accomplished in hospital by tying the extremities to the corners of the bed for as few days as can be managed. Splinting the elbows with several tongue blades, sewed in cotton cloth and tied to the arms and wrists is a helpful measure. When an infant has a paroxysm of itching it may be put in a tepid bath, or given sedatives or an antihistamine such as Elixir Benadryl. Aspirin used with circumspection is a good sedative so is a liquid preparation of phenobarbital. Sodium Amytal, a 1 gram capsule with a hole pricked in it and inserted into the rectum may prove useful in sedation and Benadryl affords valuable palliation at times.

See Fantus (J 103 1305, 1934) treatment Hill (NEngJM 213 133, 1935) allergy and skin testing Rinkel (SouthMJ 29: 807 1936) leukopenic index in identifying incompatible foods Sulzberger (JAllergy 7 338, 1936) classification and description; Hoffman and Rattner

(J 107: 494, 1936) intolerance of cod-liver oil; Hill (J 111: 2112, 1938) review; Wise and Wolf (J 111: 2106 1938) review Sulzberger (J 112: 28, 1939) topical therapy prescriptions Rappaport and Hecht (J 112: 317 1939), viewpoint of allergist Bost (CalifWM 54: 24, 1941) review; Stoesser (AnnAllergy 2 404, 1944) after improvement a child may tolerate foods previously intolerable.

Atopic Dermatitis.—The typical case of atopic dermatitis exhibits symmetrically distributed, chronic, inflammatory thickening of the dermis, with fine uniform scaling exaggeration of the minute folds, and grayish brown hyperpigmentation. Areas of predilection are the head, face, neck, upper chest and back, and the flexures of the elbows and knees. The upper half of



Figs. 1071 1072.—Atopic dermatitis ("neurodermatitis") as seen in three individuals. (Becker and Obermayer Modern Dermatology and Syphilology Lippincott, 1940.)

the body bears the brunt of this dermatitis, although in extreme exacerbations involvement may become almost universal. The surface is generally dry but may be considerably excorated because of the severe and characteristic pruritus. Hair is not lost but may be rubbed off.

Flares and remissions mark the course, which is extremely chronic. Patients are generally worse in winter months and better in the summer Flares are unpredictable and are marked by extension of involvement, increase in pruritus and swelling of the dermis until perhaps, exudation is severe and widespread. When the disease is active excoriation, secondary infection and chemical insult from inappropriate medication are likely Remissions may

be complete or almost complete One is likely to attribute remission to the last treatment tried, only to find when the next exacerbation takes place that this seemingly promising medical effort fails.

As the sufferer grows older the disease apparently abates, for the clinician sees few such patients past middle age Perhaps they have learned to care for themselves as expertly as physicians can care for them and have given up the struggle Sometimes the disease disappears for months or even years. When it does one seldom knows why but patients sometimes hit upon a climate or way of life which allows them to maintain well being

There is a relationship between flares and stress and the patient may be well aware of this (Rogerson Quart Med 6 367 1937) He will withstand pressure for a few days, then reach a breaking point. He is likely to improve during a period of hospitalization, even though treatment consists of nothing but protection and sedation There is a relationship between intensity of disease and the geographic location of the patient Some patients learn that they become much better when they remove themselves to a distant place Midwestern patients generally improve when they go westward into Colorado New Mexico or Arizona they do not usually improve in California, but Washington seems often to agree with them They do not do well when they go South or East as a rule What part of these phenomena represent psychosomatic, climatologic or allergic factors, I do not know It is certainly worth while for a patient severely affected to seek a part of the world to live in where his dermatitis is relatively mild. Yet after living there for some years, he may find that he becomes as bad off as he ever was.

CATARACT i not an extremely rare complication of atopic dermatiti , 10 of 101 cases of Brunsting (ADS 34 935 1936) were so affected. See also Peck (ADS 39: 604, 1939) Mitchell (ADS 41: 402, 1940) Carleton (BJD 53: 83, 1943); Thompson (ADS 61 433, 1950) a d Hogan (AmJOphth 36 93 1953) Juvenile cataract in these cases is likely to be bilateral, and typical of cataract associated with eczema are subcapsular anteropola hield-shaped opacities (Winkle abs ADS 41: 5— 1940) Keratoconus was seen in patients of Brereton and Baer (ADS 46: 858 194)

DISSEMINATED NEURODERMATITIS is a name for this disorder although Sulzberger and Goodman (1936) discovered no convincing evidence of psychoneurotic etiology in their study of 50 cases. In some cases there appears to exist at least a coincidence of increased tension and flare Functional studies indicated in the opinion of Van de Erve and Becker (J 10, 1098 1935) that the sufferers possess a generalized protoplasmic unrest

Psychi tric investigations by Greenhill and Finesinger (ADS 46: 19 1942) nd I sch et al. (ADS 51: 251 1945) have revealed feelings of hostility inadequacy and depression d indications of psychobiologic imbalance The mood tended to be grudgi g sorrowfully serio a tendency toward stubborn rigidity and high emot onal reactivity masked b suppression. Repressed hostil ty to the mother, a mat rnal rejection factor was emph sized b Williams (ADS 63: 545 1951), whose therapeutic approach incl ded correct on of the m ther behavio toward th child, teachi g her it basic emotional needs, the ill effect of not providing for them and the means of providing for them.

Endogenou eczema occurs in emotionally insecure individual it onset a d relapses oft n bei g precipitated by situations which threaten these person sense of security wrote Wittkower nd Edgell (ADS 63 707 1951): The distribution of the disease on the flexural surfaces and the face i representati e of the iew that the e uding kin asp res to caress or to be caressed, for the skin is the organ of contact and contact is the crucial psychodynamic need of eczematous individuals. In exh biting eczema, the patient adopt the pos tio of th uppliant whil the weeping of the eczema, like the weeping of a hild reinforces his ppeal. I do not belie e this. However I concur with their observat on that the eczematous child te ds to be eithe unwa ted or spoiled. a parent would ha dly be indiff rent to his child s chronic, miserable affliction.

Data concerned with personality and emotional f ctors obtained by Fiske and Obermayer (ADS 0 761 1954) suggested that the ps chopathologic trait of these pati ts are common to the ne rotic population of which they may be con idered a subgroup. Their basic personality structure i distingui hed by conflicting infantile eleme ts, sadistic destructive paranoid and aggressive, together with eleme ts of masochism, insecurity narcissism, sensit vity depe d ncy and ma ked sexual conflicts.

Of dermatoses and neu oses whi h i cart and which i horse i a question. What helps the adult ought to h lp the fa t with the same disease d this true of such efforts as eliminati g contactant a d ingestant provocations but is not true of psycho-

therapy Yet Walsh and Kierland (PSMMC 22: 578, 1947) helped patients who permitted several months of hospitalization more when they utilized psychotherapy than when they limited their effort to accepted dermatologic measures. See Ackermann (PsychosomM 1: 366 1939); Saul (PsychosomM 3: 66 1941); Pearson (PsychosomM 2 22 1940) Psychotherapy designed t slow down the patient and induce him to relax was elucidated by Stokes (J 105 1007, 1935) Hypnosis was beneficial in 11 of 13 cases so treated by Kartamischew (DWchr 102: 711 1936) he reported.

Excessive passivity and clinging dependency coupled with a crippling inhibition of aggressive and erotic drives, were disclosed by the psychiatric studies of McLaughlin et al. (ADS 68: 506 1953) who judged the general pattern of personality defect in atopic disease to be similar to that described for a variety of psychosomatic disorders. The pattern of the eczema pruritus-scratch complex seemed to them to be importantly related to the dynamics of depression. Stressful situations were related to exacerbations, and represented to the patient an actual or threatened disruption of emotional ties between him self and the object of his e essive dependency Life patterns showed chronic and per sisting unhealthy child parent relationships, characterized by relative or actual reject on, chi fly o the part of the mother.

If atopic dermatitis is a manifestation of psychoneurosis, it is one that is wondrously helped by cortisone.

The intelligence of the allergic child is probably neither retarded nor advanced as compared with the normal (Chobot et l: AmJDisChild 57: 831 1939) although a study of 80 children by Balyeat (AmJDisChild 37: 1193, 1929) suggested that th average i tellige ce is high. *No difference was found by Piness et al. (JAllergy 8: 169 1937)* who noted that th disease certainly handicaps to some extent.

Etiology —The disease is believed etiologically to rest on hypersensitivity Of 101 cases Brunsting (ADS 34 935 1936) reported that 71 had had in fantile eczema, hay fever or asthma. The age range was 15 to 35 years, and there was no predilection as to sex. The natural evolution of allergy dur ing the life span was reviewed by Ratner (J 111 2345 1938) While the on-set may be early the newborn period is signally free Eczema is the pre-vailing symptom of allergy in infants less than 1 year old and foods are the prevailing reactive substances. In his series, 59% of allergic dermatoses were due largely to contact with environmental substances to which the in fants reacted. The age of onset of dermatitis precedes asthma, and dermati tis is often the forerunner of asthma. After early infancy asthma is the prevailing symptom of allergy

Food sensitizations are alleged to play an important role in allergy in child hood and so also are inhalants. The presence of multiple reactivities, includ ing contactant suggests that specific therapeutic measures may fail if not all offenders are taken into account. Hill (J 103 1430 1934) believed that the cause is usually a food, even if this is hard to prove.

Atopic dermatitis Sulzberger and Goodman (J 106 1000 1936) considered to be specific vascular skin hypersensitivity to foods or environmental al lergens. Despite insistence on the etiologic relationship of sensitization, no dependable therapeutic results are obtained by removing from the environ-ment of the patient all the allergens to which he tests positively The indi-vidual is believed to have become sensitized in infancy so as to manifest in-fantile dermatitis at that period of life his sensitivity then becoming poly valent and so diffused that almost no environment is possible wherein no sensitivity exists or may develop The term environment is meant in the broadest sense to include foods and inhalants as well as plants, animals and materials. It is, however of benefit to remove as many recognizable irritants as possible.

Positi e scratch test reactions in 247 cases were studied statistically by Epstein (AnnAllergy 9: 421, 1951) wh found egg, wheat potato and milk giving th most fre-quent positive reactions, in that orde of freq ency while among environmental allergens, reactivity was most frequent to cattle, horses, feathers, house dust ad wool. Eczema was generally less sev re among those patients who did not manifest positive sc tch test re-actions. Skin testi g may be considered a valuable laboratory procedure f demonstrating etiologic factors in allergic disease when properly interpreted, concluded Sheldon et al. (J 151: 785, 1953) Tests to inhalant allergen seemed highly reliable, but skin tests for food, while sometimes being of value are often not reliable they found.

Some 90% of 136 patients had positive skin reactions to ragweed pollen, and half of these reactors had also ragweed hay fever or asthma, or both reported Tuft and Heck (JAllergy 23: 528 1952) Inhalant allergens, particularly ragweed, may cause or aggravate atopic dermatitis, they concluded.

Human dander combed from the scalp and applied in petrolatum for patch testing yielded eczematoid reactions in 11 of 1 children with eczema but not in controls, reported Simon (AnnAllergy 2: 109 1944) It contains an antigen not present in epidermis from other areas, but patients allergic to dander are allergic also to the scales of seborrheic dermatitis removed from sites other than the scalp (JAllergy 15: 338, 1944) Positive reactions are commoner in children than in adult patients, and the allergen is water soluble (SouthMJ 38 530 1945) Patients giving an immediate allergic reaction on skin testing had also a circulating passively transferable antibody to an allergen present in the normal skin. Material from the scalp is a more potent source of the allergen than from other areas, and allergen was not found in material from sebaceous cysts, lens of eye fingernail, amniotic fluid, or hair from the newborn (JIDO 11: 203, 1948) The histologic structure of the patch test reaction differs from that of natural atopic dermatitis (ADS 58: 728, 1948) Sensitivity to human dander in patients with eczema was thought to be the result of the eczema rather than the cause by Hampton and Cooke (JAllergy 12 63 1941)

Atopic individuals are often refractory to passive transfer of skin reactivity (Walzer and Bowman PSExperBiol 28: 423, 1931)

The intradermal injection of acetylcholine normally evokes vasodilation, but in atopic dermatitis there results a delayed blanching reaction which is curious and novel; yet the sweat response and the axon reflex response to this drug are not different from those of normal individuals, observed Lobitz and Campbell (ADS 67 575, 1953)

That contact dermatitis precedes atopic dermatitis in many cases was the observation of *Gaul and Underwood (AmJDisChild 80 739 1950)* who thought that this might damage the mechanisms of sweating and thermoregulation. They considered the relation between the degree of distress of the patients and the environmental temperature and humidity and found that wearing long underwear in a humid environment gave some relief. Low temperature and low humidity the critical figures being 52° F at 50% humidity caused distress.

Deficiency of magnesium in biopsies was demonstrated by spectrographic methods by MacCardle et al. (ADS 44 429 1941); see Engman and MacCardle (ADS 46: 33? 194?) Magnesium deficiency results in a derm titis in rats, but the rat disease does not resemble human atopic disease and magnesium therapy does not help the atopic patient (Sullivan and Evans: ADS 49 33 1944)

Treatment.—The first accomplishment must be the elimination of contact irritants and of these friction, soap wool corduroy laundry starch and unsuitable medicines are the most important. This measure is likewise first in infantile dermatitis. Cleansing is to be done with water alone without a washcloth, for friction is harmful. The safest topical application is petrolatum When any grease is applied thick in the ordinary way the skin feels better for a few minutes then commences to prickle and tingle, yet the sensation of dryness calls for a grease The patient may find comfort in applying the ointment, then taking a warm shower to remove the excess, then a cool rinse to quiet the itching provoked by warmth. The same amount of excitation arising in the skin is better tolerated by the patient if he is relaxed and rested. He should avoid overfatigue coffee and tea, and anxiety in so far as he can be taught to do so Coffee makes the itching worse as was noted by Fahlbusch (DWohn 105 921 1937) The patient should sleep in a warm room with few bedclothes, thus keeping the skin cool. In a paroxysm of itching a tepid bath will allay or a towel moistened with cool water and applied to the itchy parts.

Topical therapy with the usual bland agents, boric acid, aluminum acetate and the like is used. Chrysarobin ointment in 1 to 2% strength may help a chronic, stubborn area, for the skin is comparatively tough and immune to irritation in this disease wrote Wise (NYSJM 33 1321 1933) Weak coal tar ointment is often prescribed Of the antihistaminic ointments, the only one I ever use is Perazil cream, and that rather seldom. Hydrocortisone ointment 1% in a vanishing cream perhaps incorporating an antibiotic such as Neomycin or Achromycin, may be notably helpful.

Cortisone and ACTH have made the palliation of atopic dermatitis, especially of its flares, infinitely simpler than prior to the discovery of these drugs. Reports of benefit include those of Randolph and Rollins (AnnAllergy 9: 1 1951) whose patients were experimentally induced to undergo exacerbation by feeding known allergenic foods and, despite the continued ingestion of these, showed rapid clearing during short courses of pituitary adrenocorticotropic hormone therapy No ill effects were seen in 3 children given ACTH by Hestetun and Wennevold (abs J 148 77 1952) while the immediate benefits were striking Doses of from 200 to 300 mg of cortisone were used by Sternberg et al. (J 148 904 1952) at that time and they obtained remissions enduring as long as the medication was continued, followed by relapse in every case when it was withdrawn. There were no consequential ill effects. They recommended the drug for relief of severe cases.

There has been much debate regarding the wisdom of giving cortisone but the air is gradually clearing I do not withhold it and find that giving the smallest effective dose for the briefest necessary intervals of time causes no discernible harm, and accomplishes conspicuous improvement. I do not believe that relapses after withdrawal are worse than they would be if the medicine had not been used. Some patients are responsive to 25 mg per day seldom is a case unresponsive to 75 mg per day It is easy to teach the patient to take it when he needs it and to discontinue it when he has obtained respite. I have supervised its use in children over a considerable period of time—ever since its utility in palliating atopic dermatitis was first learned—and have observed nothing but good effects. It is a drug I prescribe as casually as I do thyroid with the presumption that, like thyroid, a temporary overdose can be recognized and is without lasting detrimental influences. A few years ago I wrote, No physician feels secure in his management of atopic dermatitis. That statement now requires revision. Thanks to cortisone and related drugs, atopic patients nowadays receive prompt and effectual palliation and are saved from heavy medical expenditures for Rube Goldberg medical investigations and regimes. Their gratitude would be even greater if they knew more medical history

All sorts of efforts have been tried with occasional seeming benefit fever therapy autohemotherapy injections of arsenic histamine desensitization (to which reaction may be severe Smith ADS 44 883 1941 Costello ADS 53 390 1946) liver extracts and vitamin injections (Marchmon-Robinson UCut Rev 42 912, 1938) etc. See discussion (ADS 53 656 1946)

One may justifiably try by every means to put the patient into the optimum state of health, and in this endeavor elimination of focal infection and secondary infection is indicated. Teeth tonsils and genitourinary organs should be freed from disease Anemia should be sought for and corrected if found. I seldom discover hypoproteinemia in these patients, a difference from what I so frequently detect in patients with lichen chronicus simplex. Hormonal imbalance may be looked into but thyroid and estrogenic substances generally have a bad effect on atopic dermatitis, I find.

Sunshine or ultraviolet light has a place; some patients are helped by a coat of tan Vitamin D in doses up to 200,000 units a day with appropriate alertness to intolerance (see Lupus vulgaris, treatment) helped 42 of 57 cases of Strakosch (ADS 67 496 1953)

X ray therapy in cautious dosage often alleviates the symptoms.

A move to a different geographical location may bring relief.

Mild sedation such as 0 3 Gm. aspirin each 3 hours and an occasional Seconal at night, has its place. Benadryl and Pyribenzamine may be tried and benefit accrues in about half the patients. In a severe case or recalcitrant flare of the disease the patient will respond better if hospitalized where adequate sedation and protection of the patient may be secured. He is thereby relieved of responsibility for accomplishing anything and can relax as he could not otherwise. Contactants are better escaped this way Sodium

Amytal and Demerol are effective and cool boric acid compresses may be used. Secondary infection can be better managed in hospital than on an out patient basis. Palliation with intravenous Avertin (see Pruritus) may yield welcome respite to a hospitalized patient who is miserable (Beinhauer ADS 57 1019 1948)

Elimination of intolerable foods is worth trying but this is seldom therapeutically highly remunerative The single food additive technic described for urticaria (q v) is as simple and successful as any (compare Flood and Perry ADS 55 493 1947) A paroxysm of itching may be expected to follow within a few hours the ingestion of a food allergen. Elimination of all such foods and of contact irritants has been known to relieve patients considerably Inhalants were important in the seasonal cases of Feinberg (ADS 40 200 1939) and desensitization was worth undertaking Skin tests are of little use although the scratch and passive transfer tests may afford some assistance (Goodman NEngJM 219 705 1938 Rusten MinnM 23 16 1940)

See Rackemann (AIntM 67 184 1936) review Tachau (ActaD-V 20 42, 1939) over half f atopic hildren ha e family or personal history of allergy Albert and Walzer (JID 3 119 1940) reaction to silkworm antigen different in atopic from ordinary contact reaction Zurbell (ActaD-V 21 468, 1940) transition forms combining atopic dermatitis with lichenification, urticaria, prurigo MacCardle et al. (ADS 47 335, 1943) microdegeneration findings in neurodermat tis and othe dermatoses Dithowski (ADS 48: 258 1943) egg white reacti ity on skin testing not necessarily relatod t li cal sensitivity Rackemann (NEngJM 232 449, 1945) review Nexmand (bs BJD 61 222, 1949) monograph reviewing 100 cases Hubler (ADS 59 294, 1949) emotional factors in localized neurodermatitis Tuft (JID 12 211, 1949) mport nce of inhalants Hollander (ADS 61 118, 1950) patient flared on contact w th gauze Weiner (JID 15 395, 1950) half f 10 cases responded favorably to PABA, large oral dosage given empirically, Tuft et al (JID 15 383 1950) 2 patients who flared with inhalants had impaired sweating mechanism Tuft et l. (JAllergy 21 181, 1950) inhalant case improved by hospitalization Rowe and Row (JPediat 39: 80, 1951) food and inhalant allergy good results by hyposensitizat on in 84% of cases Sternberg et l. (JID 16: 335, 1951) eosinophil response under stress different in atopic and normal indiv duals Alden (SouthMJ 44 842, 1951) treatment, Pettit (BMJ 1 79 1954) unsaturated f tty acids not effectual Witten t al (AmJDisChild 87 298, 1954) favorabl results with hydrocortisone ointment; Solomon (BMJ 1 1190, 1954) cortisone therapy unconvincing Illig (Hautarzt 5 408, 1954) topic dermatitis disappeared from paralyzed extremity in a young man who developed poliomyelitis Kesten (NYSJM 54 2441 1954) eliminat allergenic foods, inhalants, contacts, bacteria and molds, hyposensitize, use psychotherapy late ; Cornbleet and Joseph (JID 23 455, 1954) greater than normal fluctuations i lkali-acid reaction curve and delayed recovery from alkali exposure Weber et al. (JID 25: 19, 1955) abnormal acral asoconstriction on moving from cold t warm room in topic patient with dermatitis asthma, hay fever urticaria, confirming Dyster et l (JID 18 27 1952) Ingram (JID 67 43, 1955) Besnier' prurigo representative of ectodermal defect, an incurable nevoid defect of physiology

PRURIGO

Prurigo is a form of chronic dermatitis beginning in infancy or childhood persistent and extremely itchy characterized by urticarial and papular lesions occurring especially on the extensor aspects of the extremities. Broadly the connotation is nonspecific and outmoded for the name has been applied to heterogeneous pruritic diseases. Explicitly prurigo constitutes a manifestation of the atopic diseases urticaria atopic dermatitis, hay fever and asthma. Prurigo mitis of Willan is the comparatively mild form. Prurigo ferox of Hebra is the severe type rarely seen in the United States. The onset closely simulates papular urticaria chronic excoriation of which is followed by the development of small, hard, dry excoriated lichenoid papules. Intense pruritus is a characteristic feature from the beginning The anterior surfaces of the shins and the extensor surfaces of the forearms are commonly involved first. Later the eruption may become more or less generalized, but the face and the flexor surfaces remain free The hair is dull and lusterless. The skin becomes dry harsh, rough, thickened and excoriated because of inveterate scratching and eczematous manifestations may mask the true nature of the disorder Secondary infection is frequent and furunculosis may result. The inguinal axillary and epitrochlear lymph nodes are palpable even during the quiescent periods The general health is not seriously affected as a rule although the long-continued suffering and loss of sleep generally combine to render the patient haggard and wan.

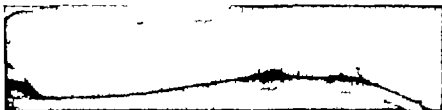


Fig. 1074.—Prurigo. (Dr Arthur Hertzler.)





Fig. 1075.—Prurigo ferox (Dr Robert N Andrade.)

Fig. 1076.—Prurigo nodularis affecting dorsum of forearm and elbow region. (Dr Anstruther Davidson.)

Etiology—The disease occurs oftenest in males (2 to 1) and lack of proper food and proper hygienic surroundings are important supplementary factors. The cause is unknown. Hebra claimed that the affection always began in infancy but Ehlers (AnnDerm 3: 861, 1892) in an analysis of more than 200 cases found the extremes of age-range were from a few days to 29 years. In 67 cases of asthma in persons less than 20 years old, Baagöe (UgeskfLaeger Feb. 28, 1924) found 13 cases of prurigo all of which had appeared in early childhood. In 12 of the 13 cases, a positive reaction to feathers, hair, pollen or food was present. The patients with prurigo mitis studied by Walzer and Grolnick (JAllergy 5 240 1934) gave atopic family histories, while this was true of only half of their cases of papular urticaria. Specific therapy suggested by the positive skin tests that were obtained proved to be without value.





Fig. 1077.—Prurigo nodularis.
Fig. 1078.—Prurigo nodularis, unusual location. (Dr Sam Sweitzer)

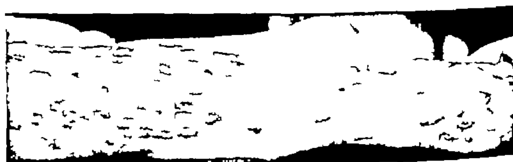


Fig. 1079.—Prurigo nodularis, extreme involvement of thigh and leg.

Treatment.—Improvement of nutritional and hygienic conditions is an important part of management, for most cases have been seen in individuals of miserable circumstances. Benadryl was effectively palliative in the patient of Zavaleta and Mom (ADS 57 998 1948) whose bibliography and review are the most recent available to me. One would expect that the same kind of management as for atopic dermatitis (p 864) including the use of cortisone, would be helpful.

See Keisler (JCutD 7 408, 1889) White (JCutVD 15 2, 1897); Holder (JCutD 29 221, 1911) Civatte (AnnDerm 7: 142, 1926), Rogerson (BJD 46: 368, 1934) psychotherapy; Questionnaire (DWchn 100 330 1935, abs YBD 1935, p. 107) Kanee (ADS 54: 112, 1946) care and bibliography

Prurigo Nodularis (Lichen Obtusus Corneus) is a rare, chronic dermatosis characterized by discrete, firm and far persistent, intensely itchy tumors which are usually

scattered over the legs and arms. Most of the patients have been women, between the ages of 25 and 60. The lesions are pea to hazelnut-sized, smooth, scaly or verrucose nodules, irregularly scattered and accompanied by intense itching. The onset of the disease is usually gradual, and the affection is an exceedingly chronic one. The surrounding skin is generally thickened and fibrotic. Removal of the growths has occasionally been followed by recurrence. The tumors range in number from 30 to 60 or more. They seldom coalesce. When fully developed they remain stationary for years.

The cause is unknown. Pautrier (AnndeD 5 897 1934) studied sections prepared with Masson s trichrome stain, which revealed that the infiltration consists of lymphocytes, histiocytes, some mast cells and a few plasma cells, that the vessels are numerous, tortuous and infiltrated, and that there exists in the cente of the nodule its periphery or even encircling it, neuroma-like masses of hypertrophied nervous tissue Large nerves were seen the fibers sheathed with collagen.

Since patients with prurigo nodularis are so rare, it is fitting to report that a woman I saw in 1953 received noteworthy benefit from cortisone, ACTH, B_{12} injections and high protein diet. She was hypoproteinemic I imagined that her dermatosis represented the concurrence of atopic dermatiti and lichen chronicus simplex.

Quite a number of years ago, Andrews recommended excision by means of high frequency cutting current, followed by roentgen therapy In one of my cases, prolonged freezing with solid CO_2 gave considerable relief although the reaction was severe, healing was slow and many lesions so treated recurred. In anothe case the lesions were excised and the wounds allowed to granulate. Lesions so treated remained cured but the patient ga e out before her nodules did. No lasting benefit ensues from roentgen therapy even if the total dose is daring

See Hardaway (ArchDermat 6: 129 1880) original description, Schamberg and Hirschler (JCutD 24: 151, 1906) 2 cases in Negroes; White (JCutD 25 388, 1907), Keister (JCutD 30 664, 1912) Williams (AmJMedSci 150 147 1915) Ahrens (DWchn 61: 853, 1920) Netherton (ADS 8: 191, 1923) 2 cases, histology bibliography; Harber (BJD 36: 22, 1924) case Freeman (ADS 11 134, 1925) case; Hasselman (DWchn 83 1721, 1926) histology; Davies (BJD 53: 143, 1941) prurigo annularis; Quiroga and Ballestero (abs YBD 1944 p. 172) allergic management; Perez and Marcuri (abs YBD 1950, p. 183) chronic allergic nodule polyneuritis of the skin Elford and Weber (BJD 63 112, 1951) remarkable case Brain (BJD 67: 24, 1955) onset in atopic woman followed penicillin intolerance.

LICHEN CHRONICUS SIMPLEX
CHRONIC LICHENIFIED DERMATITIS AND AUTOECZEMATIZATION

When the skin becomes thickened with chronic inflammation so that there is produced a fairly sharply defined patch of scaly pruritic, rebellious dermatitis, it is said to be lichenified. Papules bounded by the minute skin wrinkles are confluent in the central area, while satellite papules are seen close about the periphery The surface is generally marked into little polyangular divisions (quadrillage) representative of dermal swelling and infiltration and the effect of these on the normal skin markings. The lesion is dry although perhaps excoriated when it is relatively quiescent, and the scaling is superficial adherent and uneven. The color is brownish or yellowish from moderate melanin hyperpigmentation induced by the chronicity of inflammation, and palpable infiltration is present. Patches may be solitary or multiple and when multiple they are usually symmetrically located. Itching is persistent and severe being generally paroxysmal (Cleveland: Canad MAJ 29 368 1933)

The sites of predilection are the anterolateral aspects of the leg the dorsal proximal area of the forearm near the elbow the sacrococcygeal area and, in women especially the nuchal-occipital region. Any part of the body may be afflicted however The old, initial lesion tends to be a solid one without central clearing and circular in outline even if it is located in a place as for example on the back of the hand and fingers, where its circular shape could be recognized only if the skin were flattened out.

Lichenification may be a primary disease or it may evolve secondary to some other dermatosis (Wise JCutD 37 590 1919) Reviewing 170 cases, Cleveland (ADS 33 316 1936) commented on the fact that local pruritus may precede visible and textural alterations (pruritus with subsequent lichenification of older writers) but he was highly dubious of an alleged neurogenic

factor in etiology which has occasioned the name localized neurodermatitis, as applied to this disease (see Atopic dermatitis) The differences between atopic dermatitis and circumscribed lichenification are conspicuous (Sulzberger ADS 34 9₅4 1936 Sulzberger and Baer YBD 19₅1 p 36)

The palms and soles may be affected (Smith BJD 54 2₅5 1942) producing a clinical picture to be distinguished from keratoderma climactericum (q v) only with difficulty Lichenification of unusual appearance is occasionally seen in a place where hypertrophy of inflammatory tissue is abetted by anatomical peculiarities, as in the crotch in cases reported by Berlin (ADS 39 1012 1939) and Porter and Haber (BJD 62 2₅ 19₅0) By contrast the lesions may be small and scattered as in the patients with little nodules *of the scalp reported by Ayres and Ayres (AustralJD 1 18 19₅1)* One occasionally sees a patient in whom the disease consists of groups of firm, rounded and conical papules which are discrete rather than confluent.



Fig 1010.—Lichen chronicus simplex on l teral aspect of the thigh (Dr J Lamar Callaw y)

C rcumscribed lichenificat on sometimes starts with what appears to be infectious eczematoid dermatitis. This after a few months settles down as a onexudative persisting lesion. Acute pustul derm t t s following a dog bite evolved thus into l che old disease *of the leg in a man e h b ted by Korth (ADS 5_ 47 1945)*

Pat hy eczematoid dermatitis, intransigent to medication producing depilation in sharply defined reas not limited to the scalp was recorded by Davies and Smith (BJD 55: 39 1943) While histologically their eczema epil as wa consistent with a diagnosis of lichen simplex, the lesions eventuated in some atrophy Compare Dermatitis medicamentosa, quinacrine.

A disseminated form affecting especially th tensor aspects of the extremities may occur and the lesions are small discrete usuall excori ted and somewhat artic rial As a chro ic disease of lder patients this was described a lichen Vidal urticatus l Greither and Tritsch (Hautarzt 4 200 1953) Perhaps Gougerot tris mptomatic disease a described by Marshall and Pepler (SoAfrMJ 27 160 1953) is a related mani festation. Its 3 clin cal feat res are (1) erythematopapular lesions of from to mm. diameter resembling erythema multiforme; (2) min te purpuric macules and (3) small, discrete numerous dermal nod les These appea in crops lasting for month or more

over a period of years, affecting particularly the legs and thighs. While constitutional symptoms accompanying exacerbation may suggest periarteritis nodosa, the disease is not fatal. It has been interpreted as a nodular dermal allergide. Compare itchy purpura (p 763)

When lichenoid dermatitis affecting one leg underwent dissemination in the woman observed by Miescher (abs ADB 54: 7*0 1946), the widespread eruption was curiously distributed in segmental stripes a seemingly unique instance A linear nevus consisting of lichenification I met with, rarely (see p. 1073)

Hyperkeratosis of the dorsa of the forearms, without palpable dermatitis, was reported in several patients with disease of the gall bladder and liver by Kleeberg (abs YBD 1932, p. 170) Of his 8 patients, 7 were women, all were over 45 years old, and most of them were hypertensive. I suspect these of being *formes frustes* of lichen simplex.





Fig 1081—Lichen chronicus simplex on the leg. (Dr J. Lamar Calloway)
Fig 1082—Lichen chronicus simplex near the knee, somewhat unusual in being follicular and papular

When lichen chronicus is irritated, macerated or infected there may occur what apparently represents absorption of some kind of toxic material for an id like eruption puts in its appearance with acutely disseminating itchy erythematous or perhaps oozing dermatitis developing symmetrically especially on the flexures of the wrists and forearms, the extremities, the neck and face and elsewhere This rash quiets down and usually disappears when the primary lichenoid lesion is treated beneficially The id is likely to appear following the use of ointments, especially fungicidal ones on the primary lesion or the use of too prolonged poultices, or the administration of antibiotics, which are generally harmful rather than helpful in this disease It fades, lagging by a few days when the initial lesion improves following the use of intermittent permanganate soaks x ray therapy and cortisone or ACTH.

Etiology—Doubtless several different causes may produce lichenification. Pruritus and trauma due to scratching appear to provoke the histologic changes in eczema prone subjects. Obermayer and Becker (Trans. IX InternatDermCongr) *found* the dermal activity variable as determined by scratch tests and positive in half the tests performed, so that the response could be interpreted only as an underlying *protoplasmic* instability The synonym, circumscribed neurodermatitis, *suggests* the hypothesis held by some that

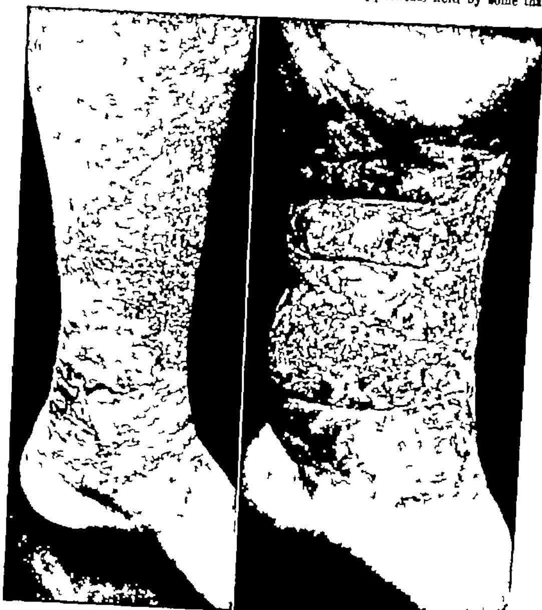


Fig 1083.—Ch onic lichenoid dermatitis with "autoeczematization. (Dr J Lamar Calloway)

Fig. 1084 —Chronic lichenoid dermatitis of the leg, associated with obesity and stasis

a psychogenic *factor* is important. Whatever causes chronic fatigue is important, I believe. Chronic contact dermatitis may become lichenified, especially if hypoproteinemia seborrheic dermatitis or medicinal irritation is concurrent *T purpureum* (q v) causes lichenoid lesions. Atopic dermatitis is lichenoid but atopic and circumscribed lichenifications are not the same (Brunsting ADS 34 935 1936) Lichen simplex and related disorders were believed to be *manifestations* of atopic dermatitis, whether circumscribed or diffuse, by Tachau (ActaD-V 20 42, 1939) a view with which I disagree.

Lichen simplex affecting the leg is often mistakenly called stasis or varicose dermatitis (see Leg ulcer) Venous incompetence may indeed be a concomitant, or even in some cases a major factor contributing to the malnutrition of the tissues of an extremity as in the patient of Heyerdale and Cannon (ADS 44 52 1941) but cases are equally numerous wherein veins are adequate and tissue malnutrition is due to agencies other than varicosity It is true that lichenified dermatitis of the leg may undergo ulceration and autoeczematization phenomena are frequently seen in association with such ulcers.

Occipital lesions, which occur almost exclusively in women, were attributed in part to irritation from the hairbrush (Molesworth UCutRev 50 61 1946) The relation between lichenification and nutritional imbalance especially with respect to anemia hypoproteinemia and hepatic function is undoubted although ill understood. I find that a high proportion, but not all, of my cases show some defect when the blood is examined with respect to the number of red cells, the quantity of hemoglobin and the total amount of serum



Fig. 1466.—Lichen chronicus simplex undergoing flare, with "autoeczematous" lesions appearing at the periphery of an old plaque.

protein. The benefit to the patient of iron, liver extract high protein diet injections of vitamin B_{12} and restriction of caffeine is frequently conspicuous, and the use of these measures has become my standard practice. To infer however what causes a disease from what usually alleviates it is, of course, highly insecure sulfonamides often but not always, help dermatitis herpetiformis; yet no one believes that that disease is caused by streptococci against which sulfonamides are also conspicuously effective.

Lichen simplex showed a disproportionate predilection for Orientals in the series of Cleveland (1936) an observation confirmed by Rein and Snider (ADS 66 612, 1952) who attributed the fact to psychogenic factors rather than to differences in nutritional habits, as I am tempted to do The chronic, disseminated case of intractable dermatitis reported by Keim et al. (ADS 58: 314 1948) improved rapidly when treated with high protein diet protein hydrolysate and parenteral plasma. These authors observed that in studying serum proteins in cases of dermatitis fluid balance studies must be made concurrently and that impairment of liver function is probably pertinent. Pro-

tein loss was presumably due to liver or kidney damage in 13 cases of erythroderma and dysproteinemia reported by Beck (Dermatologica 99 372, 1949) Dermatitis of the legs was the external manifestation in a number of patients with protein deficiency studied by Guy et al. (ADS 57 822 1948) and by Guy (ADS 61 261 1950) exemplifying geriatric nutritional eczema. The patients were responsive to therapy enabling adequacy of mastication, increasing the ingestion of protein, giving protein hydrolysates vitamins liver fractions, and hydrochloric acid with meals, correcting anemia and attending the dermal inflammatory process in a symptomatic manner The relation between eczematous dermatoses and macrocytic anemia and impairment of hepatic function was illustrated in a careful study of 2 patients by Ayres et al. (ADS 62 801 1950) who witnessed improvement in various skin diseases following therapy aimed at support of liver function.

Autoeczematization. —The phenomenon was recorded by Whitfield (BJD 34 335 1922 BMJ 2 332, 1926) Ingram (BJD 47 502, 1935) felt that in every case of eczema there is entailed some degree of autosensitization. Endogenous sensitization following local infection, discussed by Brown (BJD 51 197 1939) was exemplified by cases of scabies followed by pompholyx, ids accompanying varicose ulcers, and ids in burns and local bacterial infections Autoallergens of primary or secondary origin were accredited with eruptions resembling dermatitis venenata and dermatitis medicamentosa by Urbach (ADS 45 697 1942)

Eczema autolytica was the name applied by Smith (BMJ 1 628 1945) for sudden flares, with local exacerbation followed by acute widespread, erythematovesicular eruption and these were interpreted by Smith as representative of sensitization of the patient to his own tissues. Autosensitization dermatitis was the title used by Templeton et al. (ADS 59 68 1949) who described the typical patient as an elderly person with chronic eczema of the legs. A sharp exacerbation of the lesions takes place with extension at the periphery followed by patchy lesions on the opposite leg and elsewhere If improperly treated this generalized process persists and becomes severe sometimes attaining the proportions of exfoliative dermatitis (q v)

It is the premise that the disease must be explained in terms of something put upon the skin from the exterior which then disseminates, that necessitates hypotheses of antigens and autoeczematization. The view is equally tenable for purposes of hypothesizing that the body becomes systemically defective that the skin is therefore everywhere in an unstable state that cutaneous manifestations of systemic disease are manifested first at places where local conditions supplement general ones inciting to disease and that lesions appear elsewhere when the threshold of proclivity to the disease is lowered. Thus the interpretation of pruritus with subsequent lichenification may not seem so outmoded.

Various extracts of the patients' own tissues were used for testing by Cormia and Esplin (ADS 61 931 1950) who discovered that an aqueous extract of scales provoked a significant number of positive reactions of both the immediate and the delayed type in the patients but not in control subjects. There appeared to be a specific antigen in the autogenous epidermal cells, which, it would seem, may become antigenic in the presence of inflammatory processes under certain conditions. They (ADS 64: 31 1951) pursued investigations which suggested that eosinophilic leukocytes convey the antigen from the primary site They called attention to the fact that persons with dermatitis frequently manifest autoeczematization when seemingly normal areas of their skin are subjected to friction, burns or other irritations These are the eczema prone individuals in whom pruritus is followed by lichenification.

That an antigen responsible for cutaneous autosensitization is probably bacterial in origin was suggested by experiments of Lipschütz (ADS 68 1 8 1953) who thought the capacity for antigenicity may not be limited to one bacterial species but might occur in the species of normal flora or ordinary contaminants. Incubation of these bacteria or their products with substances derived from the epidermis appeared necessary for the formation of antigen, which seemed not to be produced, but rather to be, perhaps, transported, by the leukocytes from the site of origin to the reticuloendothelial system.

Pathology —Changes comprise hyperkeratosis and areas of parakeratosis, long narrow epidermal pegs moderate edema of the papillae and diffuse

dermal infiltration with small mononuclear cells. Pigment is increased in the epidermal cells, and the melanophages of the dermis are increased in number. Elastic and connective tissues show little abnormal change. See Sachs et al. (ADS 54 397 1946)

Treatment.—For a solitary stabilized lesion such as might be found on the proximal extensor surface of the forearm, weekly doses of 150-r x ray therapy to a total approximating 900 r may be curative. In occipital cases in women similar x ray therapy interdiction of mechanical and chemical irritation and a scalp lotion for dandruff are usually effective. One need not avoid



Fig. 1046.—Chronic eczematous dermatitis: Irregular acanthosis, spongiosis, exudation, and dermal inflammation. (Miller ADS 56 678, 1947)



Fig. 1047.—Chronic lichenified dermatitis of leg: sclerosis, acodilation, and acanthosis (Dr Fred Weidman.)

temporary epilation but epilation may not occur even when the total dose reaches 1500 r. In cases affecting the ankles, with or without ulceration, the elimination of focal infection is often indispensable. Not only teeth, gums, tonsils and genitourinary organs require consideration but also tinea of the feet and nails. Circulatory insufficiency requires medical and surgical consultations. Caffeine is ingested to excess by most of the patients I see with lichen chronicus simplex. Caffeine causes chronic fatigue (see p 886)

One must seek out and deal with anemia, nutritional deficiencies and internal medical problems which appertain. Guy et al. (ADS 57: 822 1948)

discussed nutritional aspects and cleaned up dirty mouths to improve mastication. Measures aimed at improving liver function helped eczematous patients especially those with the commonest form congestive or varicose eczema of the legs, stated Eichenlaub and Osbourn (ADS 57 171, 1948)

The basic endeavor in treatment according to Templeton et al. (1949) is to control the original area of antigen producing dermatitis, which should be kept at rest, preferably elevated while other measures are being administered.

A program which meets with gratifying success, and on which I cannot at this time improve consists of

(1) altering the diet to diminish the ingestion of caffeine which is commonly consumed in excess by these patients, and to increase the ingestion of protein;

(2) prescribing an iron and vitamin preparation, such as Bedicyte capsules, to assure adequacy in this respect;

(3) diminishing the load on the patient, securing more rest and relaxation, utilizing psychotherapy for the purpose of combating chronic fatigue and giving adequate sedation with hospitalization in severe cases

(4) applying an elastic bandage during waking hours to extremities affected with the dermatitis, a procedure which often allays itching effectively;

(5) prescribing cool soaks and compresses with potassium permanganate 5 grains to 1 gallon of water or permanganate baths in extensive cases;

(6) controlling secondary infection with Vioform cream or tetracycline ointment, occasionally with antibiotics by mouth, although they sometimes incite flares;

(7) injecting liver extract or B_{12} 500 micrograms once or twice a week;

(8) giving x ray therapy in doses larger than 75 r which do not do the job but not over 150 r (125 r being generally adequate) at intervals of from 5 to 7 days, being sure to dose the primary site while taking care not to overdose this region so as to provoke a flare

(9) utilizing cortisone 25 mg with potassium chloride 5 grains, t.i.d., if the patient is in an exacerbation diminishing to the smallest dose which yields relief maybe a tablet or two a day or none at all if relapse does not take place on withdrawal

(10) controlling contactants, for external irritation, whether by soap wool, friction, cosmetic or medication has an ill effect and

(11) pursuing the effort to put the patient into the optimum state of health by elimination of focal infection and establishment of a healthful way of living, whatever this may entail.

Intravenous plasma is especially effective in correcting protein deficiency stated Allen et al (AnnSurg 131 1 1950) but it is an expensive method if the patient is able to swallow and utilize cheap cuts of lean meat.

Other efforts in the treatment of lichenoid dermatitis include topical application of 5% crude coal tar ointment, 10% silver nitrate occlusive bandaging repeated peeling doses of ultraviolet light, Castellani s paint, etc. One may apply 25% potassium hydroxide scrape off the scales and dress the lesion with Ichthyol ointment. Peck (1947) told me he used pure coal tar for a few days alternating with zinc paste occasionally blistering a lesion with solid CO An ointment containing 3% crude coal tar and 5% ammoniated mercury sometimes is quite effective Axel (1953) showed me The application of 20% podophyllin in tincture of benzoin once a week may yield good effect in the dry occipital cases (Belisario AustralJD 2 18 1953)

Hydrocortisone ointment 1 2.5% generally helps circumscribed lesions, (Sulzberger et al. J 151 465 1953) Intradermal injection of hydrocortisone the injection aided perhaps by adding hyaluronidase, may be tried with good hope of success. Elastoplast occlusive and supportive dressings, reapplied weekly may prove helpful (Kulchar ADS 40 1000 1939)

Stokes (J 105 1007 1935) stressed psychologic aspects of treatment giving suggestions as to how the patient may be induced to slow down.

It is interesting to note that these patients are often made worse by thyroid thyroid-stimulating hormone or estrogen, in my experience. I gave gamma globulin in large and expensive doses to 1 patient, and it did no good.

See Knowles et al (ADS 31 38, 1935) threadlik wrappings boat roots of hairs extracted from occipital cases Tulim and Squires (ADS 43 [illegible], 1941) insulin shock therapy Pels and Ellis (ADS 64 677 1946) alcohol injection in localized cases, a used for pruritus

and by Stone (BullJHH 27: 242, 1916); Lutz (abs YBD 1949 p. 141) therapeutic importance of gaining insight into patient's mental conflicts, prescribing calcium glycerophosphate, mild tar ointment and x-ray therapy; Lynch (ADS 60 307 1949) suboccipital cases; Garb (ADS 61 690, 1950 62, 841 1951) podophyllin topically, dangers; Fowlkes (SouthMJ 43 54, 1950), psychomanagement, Lynch and Enlyely (J 147 118, 1951) hypoproteinosis, Morgan (JMoMA 49: 896, 1952) dermatologic manifestations of hypoproteinemia, lichenoid dermatitis of leg helped by feeding meat Baboario (Proc 10th Internat. Congr Dermat, 1952) eczema and autosensitization, review; Seitz et al. (JID 20: 263, 1953) patient with circumscribed neurodermatitis has punitive superego, tends to express aggressiveness masochistically Hellier (BMJ 1: 504, 1954) forearm contact dermatitis from armchair simulating lichen simplex Wells (ADS 70 178, 1954) in eterate rough patch on leg diagnosed lichen corneus hypertrophicus of Pautrier

EXUDATIVE DISCOID AND LICHENOID CHRONIC DERMATOSIS

A dermatosis of unknown cause, sudden onset and intransigent course, occurring principally in Jewish males of 30 to 50 years of age, was described by Sulzberger and Garbe (ADS 36: 24 1937) The widespread eruption is often preceded by circumscribed dermatitis which is readily irritated by efforts at treatment. Pruritus is a prominent feature, worse at night and with crises accompanied by chilliness and paresthesias. Sharply demarcated oval and discoid plaques of rapid variation in consistency and appearance are seen. They may be flat and scaly elevated and edematous, or oozing and crusted. Vesicles are evanescent but punctate oozing with vesiculation of histologic dimensions occurs. While no area is exempt, predilection is evinced for penile scrotal and extensor surfaces and the perimammillary circum ral, abdominal and scapular regions.





FIG 1038.—Exudative discoid and lichenoid chronic dermatosis, typical discoid and lichenoid lesions. (Dr Marion B. Sulzberger)

FIG. 1039.—Mid-chest region, with oval, scaly lesions somewhat simulating pityriasis rosea. (Sulzberger and Garbe ADS 36 247 1937)

Rosen (ADS 32: 963, 1935) was accredited with having identified a case presented by Kaufman as belonging to a distinctive group: In cases of this type the patient's first symptoms are those of an acute dermatitis, dermatitis venenata or allergic dermatitis, the redness swelling and vesiculation usually involving the face and neck and gradually spreading to other parts. After a few weeks the acute symptoms subside; the involvement becomes more or less generalized, and the eruption presents the features of a universal toxic dermatitis such as a dermatophytid. A few weeks later the picture changes, and there is a uniform desquamation which closely resembles that seen in cases of pemphigus foliaceus. When this edematous condition subsides, there are present all over the involved area distinct infiltrated lesions which suggest the infiltrative stage of mycosis fungoides. When these regress the eruption consists of disseminated scaly lesions not unlike those of psoriasis.

The exudative and discoid phase is marked by discoid or oval plaques or patches of different sizes and shapes, fairly sharply demarcated and without a tendency toward central clearing passing through the stages of minute vesiculation, superficial oozing and crusting, and later scaling and lichenification. Erythema is never marked. Sometimes the lesions are edematous, sometimes almost macular They are irregularly scattered over the entire skin except the scalp, palms and soles, in some areas sparse and in others closely grouped. Later a lichenoid phase is attained, during which weeping is absent or much less marked. Cutis anserina is noteworthy when the patient is exposed. Not only are

isolated lichenoid papules to be found but also large areas of skin may be palpably thickened, showing accentuation of the normal skin markings, but this thickening undergoes rapid changes in consistency. A later phase is often seen resembling the premycotic stage of mycosis fungoides, the infiltration of the discoid and oval lesions dominating the picture. During the whole course of the disease the patient complains of showers of pruritic, urticarial lesions lasting from several minutes to several hours, the lesions bearing some



Fig. 1090.—Typical discoid and lichenoid elevated plaques and diffuse lichenification of posterior axillary and arm region. (Drs. Marion B. Sulzberger and William Garbe.)



Fig. 1091.—Exudative discoid and lichenoid chronic dermatosis on the sol[illegible] re deeply seated, sterile, papulovesicular lesions. (Sulzberger and Garbe: ADS 36: 247, 1937.)

resemblance to those of prurigo. Sulzberger (YBD 1950, p. 289) was able to say that he has seen more than 100 cases in the past 15 years, and lymphoblastoma had developed in none of them.

I have yet to see what I should diagnose as a case of Sulzberger and Garbe's disease. Descriptions of it are reminiscent of autoeczematization in hypoproteinemia (p. 874). Response to cortisone therapy was noted by Kanof (ADS 70: 625, 1954).

X ray therapy has been known to aggravate the symptoms, and the disease did not respond to arsenic or anything else the original authors tried. Laboratory studies revealed slight eosinophilia. Serum proteins were not tested. Sections showed edema, capillary and arteriolar dilation, periarteriolar infiltration with inflammatory cells, not with those of mycosis fungoides, irregular acanthosis, spongiosis, and some intraepidermal vesiculation (Sachs and Kirsch: JID 8: 215, 1947). The patient of Comperus (ADS 54 374, 1946) was worse in the winter. Coal tar ointment relieved a patient of Bernstein (ADS 41: 1185 1940). Pascher (ADS 4.: 222, 1940) thought subcutaneous sodium arsenate helpful in 5 cases. Contactants were believed causative by Cannon (ADS 36 1260 1037; 48: 669 1943; 55: 273, 1947) and by Sharlit (ADS 45 776 194.)

See Wright (ADS 38: 134 1938), case; Wise (ADS 40: 287 1939) case; Gross (ADS 43: 847 1941), questionable case in child; Costello (ADS 51: 145, 1945) case; Kocsard (JID 10 1, 1948) 3 cases, quoted Ramel (BJD 49: 307 1937) as having described similar "neuropathic eczema. Andrews (ADS 60: 1004, 1949) case; Costello (ADS 53 359, 1940) case.

CHRONIC DERMATITIS OF INDETERMINATE CAUSE

Confusing Exudative Dermatitides, once called eczema, are described under streptococcic dermatitis, staphylococcic dermatitis, dermatitis venenata and its complications (q v) dermatomycosis and dermatophytids, lichen chronicus simplex, and atopic dermatitis. Having distinguished these conditions, little remains of the classic but outmoded diagnosis of eczema.

When dermatitis persists, the practical attack may be based on the presumption that something interferes with healing for the tendency to heal may be trusted. The search for interfering agencies must take into consideration mechanical factors, primary irritants and allergenic contactants, secondary infection, focal infection, medicinal and food allergy psychosomatic problems, and inadequacy of tissue nutrition which may be due to defective circulatory nutritional, endocrine, renal, hepatic or hematopoietic function. It is usually possible to eliminate such factors systematically and so to obtain cure or alleviation.

Chronic Dermatitis of the Hands and Feet.—This topic is considered also under the title Recalcitrant pustular acrodermatitis, q v Much material is pertinent in the sections on dermatitis venenata, infectious eczematoid dermatitis, and lichen simplex chronicus. What hereinafter is said about hands may be applied with only slight alteration also to the feet, where contactants appertain mainly to cleansers, hose, shoes and medicines rather than to the more numerous items affecting the hands. The dependency of feet makes them subject to mechanical deficiencies of circulation to an extent greater than the hands are.

Dermatitis of the hands (Sutton and Ayres ADS 68 266 1953) is a subject worthy of monographic presentation, comprising conditions which give rise to an immense amount of suffering and which constitute some 9% of the daily medical endeavor of a practicing dermatologist (Lane et al. J 128 987 1945) The usual patient is a young matron, who must keep house cook, wash dishes, do the laundry raise her children and hold her husband. She can ill afford to sustain the misery of manual disability and her occupation is inherently one of the most hazardous with which the dermatologist commonly has to deal (Jordon et al. J 115 1001 1940)

If one should write book on dermatitis of the hands, it might w ll co tai chapters on general considerations of anatomy embryology physiology symptomatology pathology etiology diagnosis, and treatment. These would be followed by essays on dermatoses due to physical agents, chemical agents, and parasites of the various sort; derm toses represent i ve of disordered metabolism, vascular fu ction, neurologic nd psychic function trophy and pigmentation, and growth disorders of m lform tion d neoplasia. There would be ecessarily thick chapte devoted to disorders of as y t u determi ed cause.

PERTINENT CUTANEOUS ANATOMY —The skin as a whole is th dividing line between th person and his environment. It combines the features of a barrier an adaptive mechanism, and a sensory organ—a great deal is asked of it so to speak. It keratin coati g i relati ely inert, impervious to water and resist t to acids, but it is less resista t t lkali, under the influence of which th cell bodies swell and loosen from one another The skin f the hands anatomically is characterized by a sparseness of tissue that kin elsewhere does not manifest. There is no skin to waste

The volar epidermis, which extends over the sides of the fingers, comprises a large proportion of the total epidermal tissue of the hands and is extremely thick. It is richly supplied with sweat glands, but hair and sebaceous glands are absent. The sweat ducts are tiny; they coil their way through the thick epidermis and are vulnerably fragile. A loss of volar epidermis requires longer to heal than a loss of similar area in a location where the epidermis is thinner. When epidermis is damaged and epithelial cells swell *and burst some by-products of dead epidermis must be absorbed.* When volar epidermis is the site of such a process, there is a great quantity relatively of altered epidermal material available for absorption and it would seem that the absorption of it results in damage of a toxic sort to epithelium distantly located, for vesiculating disease of the soles induces vesiculation of the palms, and vice versa. Phenomena of autoeczematization may so come into play (see p. 8 4).

Pertinent Cutaneous Physiology.—Physiologically the skin, as a protective mechanism, in addition to its physical properties supports a constant flora of nonpathogenic organisms and is liable to the influx of pathogens. If the skin is dry and cool, pathogens cannot thrive and drying is one of the mechanisms of self-sterilization (q.v.). The impossibility of attaining a state of coolness and dryness of the skin explained the impossibility in the tropics of curing the coccic infections which caused many casualties in World War II.

The hands have *less latitude in accommodating themselves to environmental temperatures* than other parts because they are not massive and because they offer a large surface per unit of weight of exposure to their surroundings. Their skin is frostbitten, sunburned and macerated in a manner to which skin located elsewhere is not subjected.

As an organ of sensation the skin is of great significance for it mediates the psyche with the physical world by means of tactile pain and temperature sensibility, and the hands embody the most highly developed, discriminatory sensibility of any part of the skin. Psychosomatic influences and relationships are therefore highly significant in some cases of dermatitis of the hands (Stokes et al.: J 123 195, 1943). The hands are busy if the mind is busy. The hands are agitated if the mind is agitated. They pick at, pry at, rub, and investigate and they do these things not only to external objects but to themselves. The patient with dermatitis of the hands is much tempted to move, flex, and extend his fingers to test the sensibility of his hands, and to keep inflamed tissues continually in motion and *if he is worried he does it the more. Sweating* is in part controlled by sympathetic nervous influences, and the tense and anxious person has cool, wet palms. Sometimes the volar skin actually drips perspiration. Such persons are more than normally susceptible to maceration and to bacterial and fungous infections and are subject to recurrent and recalcitrant attacks of fine vesiculation, pompholyx (q.v.) and secondary infection thereof.

Mechanisms Provoking Dermatitis.—Inflammation is a vascular activity not fundamentally different in skin than in other organs. Immunity is a function of inflammation, and allergy is a variant of immunity representing in the broad outlook a failure of successful immunity. Contactant allergy is an extremely important factor in skin diseases in general, and because of the *function of the hands as organs of touching and doing* their skin is subject, more than skin located elsewhere to its development. The skin of the hands is exposed to the potentiality of diseases provoked by heat, cold, light, moisture, irritant chemicals, sensitizing chemicals and pathogenic organisms to a degree over and above other skin. It is subject additionally to all the diseases of internal origin that skin is elsewhere and the hands are especially subject, being special tactile organs, to psychosomatic disturbances.

The *mechanisms provoking inflammatory* skin disease of the hands are at least 10 in variety

1. Trauma of all kinds including friction and excoriation.

2. Contactant injury by primary irritants, which provoke changes like those induced by trauma and which heal similarly.

3. Contactant injury by sensitizers, which alter the reactivity of the skin more or less permanently so as to provoke itching, redness and vesiculation when the skin is touched even by minute concentration of the irritant.

4. The mechanisms of injury by chemical substances absorbed and provocative of intoxication of allergic reactions such as dermatitis medicamentosa, including fixed eruptions, or of food allergy.

5. The mechanisms of locally invasive parasites, including viruses, bacteria, and fungi, *as well as animals such as Acarus scabiei.*

6. The mechanism of focal infection which influences the distant site perhaps by supplying circulating parasites or by-products of parasites to be filtered out by an already existing inflammatory reaction, or perhaps by supplying parasites which reach the skin via its surface so that the flora continually contains pathogens.

7 The mechanisms of nervous and mental, or psychiatric, abnormality including anxiety neurasthenic fatigue, excoriation and self-mutilation.

8. The mechanisms of cutaneous changes due to nutritional deficiencies, metabolic defects and hormonal imbalances.

9 Lowered resistance of the individual, rendering the skin susceptible to inflammation or infection. While this is ill understood and may be pertinent to heredity (diathesis) psyche, nutrition, or foci of infection (Barber: BJD 42: 500 1930) it is evidently a reality which teases a mind that seeks explanations, and it demands some sort of recognition.

10. Combinations of these mechanisms.

ETIOLOGIC CLASSIFICATION OF DERMATITIS OF THE HANDS.—PHYSICAL AGENTS, including trauma, friction, excoriation heat, cold, moisture and maceration, and radiation (actinic roentgen, or radium) may be listed. Etiologic diagnoses, respectively would include for example cuts, bruises, crushing injuries, chapping, burns, frostbites, sunburn, and roentgen ray dermatitis and atrophy Treatment for such dermatitides must include elimination of further action of the noxious agency appropriate alterations of environment of the hands, and palliative protection while the skin is allowed to heal as well as it can. Restorative efforts appropriate to some cases include plastic surgery

The defatting and drying effects of soap and the detergents, as in washing dishes, especially during cold weather frequently initiate an eczematous eruption of the hands, which may be further aggravated by any one of many common household irritants, such as bleaches waxes, polishes and, often enough, hand lotions and cold creams. Secondary infection, especially with micrococci, is likely to follow

CHEMICAL DERMATITIS, EXTERNAL.—*Chemical Injuries* include the effects of primary irritants and of sensitizers. The etiologic diagnosis is dermatitis venenata (q v) Treatment requires elimination of contact with injurious chemicals, palliation of symptoms, and prevention of secondary infection while the skin heals.

The differential diagnosis between contact dermatitis and dermatitis of the hands from internal causes is not always easy In general, contact dermatitis is more likely to involve the backs of the hands, the backs and sides of the fingers, and the interdigital webs, whereas eruptions of internal origin are more frequent on the palmar surfaces. Exceptions, however are provided by substances to which the hands are sensitive and which are grasped, such as nickel, rubber or plastic handles, rubber hose and kitchen-knife handles.

A common history is that of an eruption beginning on the left fourth finger under rings and later spreading to other portions of the hands. This eruption is evidently initiated by the retention of dish washing soaps or detergents beneath the rings as the result of inadequate rinsing Then the injured skin is invaded by bacteria, usually *Micrococcus* ex which maintain the disease even if irritating chemicals are avoided.

Id Reactions may produce eczematous eruptions of the hands. The id reaction is probably a type of allergic response and is most commonly seen on the hands after an acute dermatophytosis of the feet, but a microorganism is not necessary for the production of an id reaction. A severe chemical dermatitis of the feet may produce an id eruption of the palms, and vice versa.

Keratolysis Exfoliativa.—The lesions are small rounded peripherally expanding shallow scaling macules affecting volar skin, initiated by tiny tender or itchy presumably vesicular puncta occurring in crops. While it is possible that in some instances this condition represents dermatitis venenata there is general agreement with MacKee and Lewis (ADS 23 445 1931) that it is usually a dermatophytid. It has been known to depend upon fungous infection of the vagina as well as of the feet.

CHEMICAL DERMATITIS OF INTERNAL ORIGIN may be caused by hypersensitivity to chemical substances ingested, inhaled or injected (see Dermatitis medicamentosa) by allergenic foods (Livingood and Pillsbury ADS 60 1090 1949) by nutritional deficiencies in vitamins or protein by endocrine disorders of oversupply imbalance or deficiency, and by metabolic chemical errors. Treatment for such diseases requires elimination of allergens, adequate re-

placement of such necessary drugs or foods as must be eliminated addition of adequate vitamins or other nutrients, and correction of endocrine imbalance or metabolic error so far as this can be achieved along with palliation and prevention of complications.

Atopic Dermatitis while usually flexural, may affect the hands predominantly It is a dry disease unless it is secondarily infected occurs on the dorsa of the hands and fingers, tends to relapse in the winter season, looks like atopic dermatitis (p 861) and responds to cortisone by mouth and hydrocortisone ointment.

Food Allergy—This is perhaps a fa tor in a small percentage of cases of dermatitis of the hands. Winston and Sutton (ADS 58 335 1948) thought that they identified food allergens as causative dermatitis with fairly characteristic features. The eruptions are persistent with flares. They are located on the dorsa of the hands a d about the wrists. They are dry nonvesicular and lichenoid and are roughly circular The typical feature is the presence of gouged-out excoriations, which are made by the patient during his sleep, for he can refrain from digging his hands when he is conscious. Winston was not able to confirm the belief of Flood and Perry (JID 7: 309 1946; ADS 55: 493, 1947) that food intolerance can evoke vesicular eczema. Identification of causative foods was accomplished, not by scratch tests or elimination dieting, but by the single-food additive diet. In this the patient eats one food during 24 hours, after which the hands are examined for the presence or absence of telltale excoriations. If these are absent, the food is adjudged innocuous and another food is added to the allowance of ingesta. When a food is added and is followed by itching and gouging it is judged probably injurious a d is omitted from the diet for some time later it is retested. Thus one proves, after careful observa tion, which foods are harmful and which are harmless.

I am presently of the opinion that food allergy is an extraordinarily uncommon cause of dermatitis of the hands.

Nutrition.—Vitamin deficiencies provocative of dermatitis of the hands are typified by pellagra There are however occasional unrecognized cases of vitamin B deficiency sometimes associated with macrocytic nutritional anemia, in which eczematous dermatitis of various types suggests pellagra (Stryker and Halbersen ADS 51 116 1945) Rarely are the hands exclusively involved, although cases are not rare wherein the hands are involved along with other parts of the body Vitamins other than the B complex are seldom critically concerned with dermatitis although Gross (ADS 44 1060 1941) would associate nummular eczema its winter exacerbations, and asteatosis with the need for vitamin A, which he gave to 24 patients with benefit to 18 of them.

The relation of protein nutrition to chronic lichenoid eczematoid dermatitis (p 873) is important. In many patients with such dermatitis, the total serum protein has ranged from about 5 6 grams per 100 cc. to 6 4 grams, and the patient has improved on a diet high in protein cortisone injections of vitamin B and restriction of caffeine.

Impaired liver function is often associated with disturbed protein nutrition A number of instances of hyperkeratotic dermatitis of the palms as well as other dermatoses including scattered localized neurodermatitis, nondescript eczematous eruptions, and severe flexural dermatitis have been encountered during the past several years in which impaired liver function was revealed by the sulfobromophthalein (Bromsulphalein) test (Ayres et al. ADS 62 691 1950) The condition usually responded satisfactorily to a program of low fat high protein, adequate-carbohydrate diet, abstinence from caffeine and alcohol, administration of a crude liver extract containing folic acid in a dose of 2 cc (2 I U per cubic centimeter) once a week, use of a high-potency vitamin B complex and oral administration of a lipotropic substance (Methischol which contains *dl*-methionine choline and inositol together with the natural B complex from liver)

Parasitic Infections.—*From the Exterior* infections with viruses, rickettsiae bacteria fungi protozoa or metazoa are exemplified by such diseases as warts, rickettsialpox micrococcic or streptococcic impetigo, or a mixed form infectious eczematoid dermatitis, carbuncle diphtheria cutis, anthrax,

even primary tuberculosis of the skin, and syphilis, dermatomycoses due to specific fungi, oriental sore and amebiasis cutis, and metazoan parasitic diseases ranging from schistosomal swimmers itch through myiasis, scabies and tick bites.

Superficial fungus infection of the hands is relatively rare in spite of the frequency with which this diagnosis is made. The diagnosis should be made only after the organism is demonstrated by direct potassium hydroxide mounts examined microscopically or by culture on Sabouraud s medium (Mitchell: ADS 19: 659 1929; J 146: 541 1951). The commonest fungus affecting the hands in the western part of the United States is *Trichophyton purpureum (rubrum)* and it usually attacks both feet and only one hand, frequently also involving the nails. The eruption is ordinarily inconspicuous, consisting of fine, dry scaling with slight erythema, usually affecting the palm but sometimes extending to the dorsal aspect. It is indeed recalcitra t to treatment. Yeastlike fungi, usually *Candida (Monilia) albicans* occasionally ttack one or more interdigital webs, producing a red, glazed appearance with slight peripheral scaling, and they also may cause chronic paronychia, especially in persons whose hands are wet much of the time.

If all the influences adverse to healing including parasites, can be sufficiently impeded and when sufficient time has elapsed, the patient gets well. A patient heals himself if circumstances are favorable and if he has the capacity He cannot be forced to get well.

Therapy appropriate to parasitism may be made highly specific, topically or systemically in an effort to make life hard for the parasite and easier for the host. Identification of parasites is essential to optimal treatment, smears, cultures, dark-field examination, serologic and immunologic tests, tests for ant biotic se sitivity and animal inoculatio s being utilized. Few parasites nowadays re resistant to every known antiparasitic chemical substance. Cool, dry illuminated skin does not support flora as does warm, moist skin in the dark.

Parasitic Infections from the Interior Comprising Focal Infections—Significant foci may exist in teeth gums tonsils sinuses, prostate cervix bladder gastrointestinal tract and even distant sites of skin disease (Barber Proc RoySocM 26 329 1933; Andrews et al ADS 29 548 1934) Focal infection is simple to comprehend biologically it is a commonly occurring host parasite relationship wherein pathogenic organisms are located in a circumscribed lesion from which they can be eliminated only by the performance of a mechanical alteration such as an extraction, excision or plastic repair

If the concept of focal infection is debatable, the compelling argument in its favor is the fact that many a patient gets well when foci, as I have defined them, are removed.

Such parasitism persisting locally makes pathogens and their by prod cts constantly available for influence upon, o invasion f, other tissues of th host when opportunity offers. In pyorrhea, streptococci and staphylococci are present and ready to i fect the skin once it is damaged by let us say contact dermatitis. Focal infections provide f r the continual presence of transient pathogens among the skin flora; for when ny part of the body is infected with streptococci, pathogens are plentiful on healthy skin areas (Martin: BMJ 2: 245, 194.)

Not only may foci of infection feed pathogenic bacteria into the circulation and finally into damaged skin, but such foci perhaps may also lead to sensitization of tissues elsewhere so th t the products of focal bacterial growth enter the circulation and upon reaching previously sensitized tissues result in various pathological entities, as, for example chronic rticaria.

Diagnoses exemplary of dermatitis due t focal infection incl de recalcitrant pustular acrodermatitis (q v), and, in ma y cases, simply chronic dermatitis of the hands (Sutton: JAMA 46 410 1949)

The treatment of such conditions requires adequate search for and elimination of foci, and the dermatologist welcomes especially the assistance of competent dental genitourinary and gynecologic consultants. The elimination of foci by extractions, oral hygiene tonsillectomy pelvic repair cauterization of the cervix, prostatic massage or even diligent dermatologic attention to pedal dermatomycosis, onychomycosis, or seborrheic dermatitis of the scalp (which may indeed serve as a chronic source of failure to cure dermatitis elsewhere)—such elimination of parasitism limited to small regions, but deleteriously influential upon distant areas, makes sense in theory and succeeds in practice.

Parasitic Infections from the Interior Comprising Systemic Disease with Cutaneous Manifestations require discussion when one is considering all possible dermatitides of the hands. Each kind of parasite affords exemplary possibilities of specific etiologic diagnoses viruses, and recurrent herpes simplex or brachial herpes zoster rickettsiae and Rocky Mountain spotted fever bacteria and scarlatina tuberculosis, and syphilis fungi, and tinea blastomycosis or coccidioidomycosis protozoan infections and leishmaniasis and metazoan infections such as trichiniasis. Successful therapy requires painstaking etiologic diagnosis and then appropriate specific and supportive efforts.

DERMATITIS OF UNKNOWN ETIOLOGY is exemplified by such diseases as the following which may influence the hands atopic eczema lichen chronicus simplex, lupus erythematosus, granuloma annulare psoriasis, lichen planus, erythema multiforme scleroderma and acrosclerosis. In the treatment of these after one has made the diagnosis, which may require histologic study empirical therapy offers a good deal.

Pompholyx (Dyshidrosis) must be included in the discussion of eruptions of the hands. Much confusion exists concerning the nature of this condition but its clinical characteristics are fairly typical. The eruption occurs usually on the palms and/or soles and on the sides of the fingers Initially the process is relatively noninflammatory consisting of tiny deep-seated, sago-like vesicles occurring singly or in groups. Later possibly as the result of secondary infection or irritating medication, the condition may become eczematized and may lose its original character Benedek (IndustM 16 134, 1947) believed that pompholyx is due to a micro-organism normally indigenous in man, *Bacillus endoparasiticus* which under ordinary circumstances causes no clinical manifestations but which as the result of a disturbance in the immunoallergic balance can be brought into activity manifested in the form of pompholyx. He believed that contact dermatitis may be such a disturbing facto and he so explains why proved industrial dermatoses of the hands may continue to manifest activity long after all sources of contact irritants have been eliminated. I prefer to think of such cases a being due to secondary parasitism, focal parasitism, nutritional deficiency medicinal irritation, and psychosomatic influences in various etiologic combinations. He stated that many cases of prolonged or recurrent pompholyx may be brought under control by a series of intradermal injections of *B endoparasiticus* vaccine. His ideas have received little acceptance but in the absence of any definitely proved cause of this stubborn dermatosis (sweat gland obstruction being another theory) perhaps final judgment should be deferred. Ayres has felt that favorable results have been obtained in some obstinate cases with a course of Benedek s vaccine given in 4- or 5 week intervals in a continui g dose of 0 1 cc. intradermally

Pompholyx would seem at times to be a manifestation of atopic dermatitis. Cortisone fairly reliable for its palliation. See p. 165.

Herpetoid (Nummular) Dermatitis was segregated as a distinctive type of chronic dermatitis of the hands by Pollitzer (JCutD 30 716 1912) It attacks the dorsal surfaces of the hands or other parts of the extremities. Round or oval patches appear 1 to 5 cm in diameter consisting of groups of vesicles or vesicopapules The itchy efflorescence slowly recedes and heals, but may recur abruptly several times a year in approximately the same location Sharp demarcation of the eczematous patches is notable (Chipman ADS 32 603, 1935) Worse in winter and aggravated by friction and alkali as a rule the condition may be helped by administration of vitamin A (Gross ADS 44 1000 1941) or by vitamin A combined with high protein diet and protection against cold, wind friction, irritant chemicals and secondary infection (Gross NYSJM 51 2025 1951) It is recalcitrant to local medication other than hydrocortisone like pustular acrodermatitis, although x ray therapy will sometimes cause its temporary disappearance Improvement of most cases and cure of some were obtained by Schoch (JChemother 15 36, 1938) by the use of sulfanilamide Chronic prostatitis seemed a rather common etiologic focus reported Carpenter (USNMB 47 453 1947) and his patients were helped by penicillin and prostatic massage The disease was interpreted as a fixed type of exudative neurodermatitis by Cope (SouthMJ 45 612, 1952) whose treatment included avoidance of contactant irritation sedation, tar preparations topically elimination of focal infection and food allergies, administration of vitamins, and the trial of bacterial antigens and hormonal therapy The etiologic complex includes poor nutrition bacterial allergy and

bacterial invasion, thought Fowle and Rice (ADS 68 69 1953) In these cases I give especial consideration to mechanical irritation, wool and an atopic background, and manage them in accord with the principles applicable in chronic dermatitis of the hands of undetermined etiology

Hyperkeratotic Dermatitis of the Palms.—Lichen chronicus simplex (q.v) of the palms and soles was described by Smith (BJD 54: 255, 1942) Also within this class is an entity resembling keratoderma climactericum (q.v) but not occurring exclusively in women. All my patients have been adults, the majority of them beyond middle age. Their occupations have been widely assorted, but many of them have been housewives. The lesions are sharply circumscribed, hyperkeratotic, and nonvesicular (Ayres and Anderson: CalifWM 56: 63, 1942; Sutton and Ayres: ADS 68: 266, 1953) They are homogeneous within their borders and arcuate in outline. They are intensely pruritic and sometimes painfully fissuring They are generally roughly symmetric in distribution affecting especially the midpalmar region, and are also *occasionally scattered on the vola and lateral* aspects of the fingers. A brilliant, greenish-white crisply demarcated fluorescence is seen under illumination with Wood's light. Scrapings nd cultures have not yielded positi e bacteriologic or mycologic findings, although the lesions of several patients have yielded species of Hormodendrum, the pathogenicity of which is of course questionable. The histologic structure, with parakeratosis and fairly intense superficially located, leukocytic infiltration of the dermis, resembles somewhat that of psoriasis. Yet psoriatic lesions are not present elsewhere on the bodies of the patients. In this particular kind of circumscribed, pruritic, hype keratotic dermatitis of the palms, one does not observe the sudden



Fig. 1092.—Nummular eczema of hand.

flare phenomenon which occurs in a toeczematization (q.v) a phenomenon characterized by widespread, erythematous and vesicular rash typically associated with lichen chronicus simplex under the inf ence of irrit tion, maceration or secondary infection. This hyperkeratotic dermatitis remains dry and limited to the palms, fi gers and distal vola skin of the wrist.

Lichen chronicus simpl x, indeed, may occur on the hands rarely but when it does, the dorsum f a h nd and som of its fingers, unilaterally and pe haps the fl xure of the wrist are affected. Lichen chronicus simplex is a deeper disease with greate dermal infiltration less prone t undergo fissuring and more prone to exhibit excoriation.

One may safely recognize the existence of a class of dermatoses involving the palms which is charact rized by hyperkeratosis, often with itching fissuring and, i some cases, erythema. Among such cases one sees various grades of these various features, so that it is difficult to decide whethe there exists among them a subgroup with a specific clinical pict re. I lean toward the view that a specific picture may be drawn, deli eated by the features of harp margination; lesions which are oval, homogeneous, and superficial; absence of vesiculation presence f marked pruritus; unresponsiveness to mere control of contactants; bsence of the a toeczematization phenomena which often accompany lichen chronicu simplex and lack of the thickness and the occasional moist re of this condition; distribution of peculiar limits, and manifestation of an i teresting fluorescence in Wood's light. These patients re often hypoproteinemic, a d they generally show a favorable response to cortisone a d i jections of B_{12}

NONINFLAMMATORY DERMATOSES OF THE HANDS.—Not to be construed as, strictly dermatitis are numerous other dermatoses often affecting the

hands, such as epidermolysis bullosa, keratosis palmaris hereditaria, keratoses, and carcinomas. Metabolic disorders, such as acanthosis nigricans and xanthoma, seem to belong in this classification rather than with dermatitides due to internal chemical influences.

COMPLEXITIES OF ETIOLOGY.—Dermatitis of the hands is not often due entirely to one mechanism. Assume for example an inflammation resulting from excessive exposure to sunshine. Redness and vesiculation follow, new epidermis is supplied from beneath, epithelization becomes regular after a period of irregularity manifested by scaling, the dermal reaction is reversible and fades in due time and the skin again becomes normal. But complications are possible. An unfortunately chosen sunburn remedy might act as an irritant. The person would then have his physical injury plus superimposed dermatitis venenata. The lesions easily could become infected with pathogenic micrococci, and he then would have bacterial dermatitis as well. He might, therefore, be given injections of penicillin and break out with dermatitis medicamentosa. If his luck continued bad, his pyorrhea might serve to reinfect his dermatitis more or less continuously. Then he might be given some x-ray therapy, improve for a time, relapse, receive more x-ray therapy repetitiously and eventually suffer x-ray burns. A conceivable sequence of events in a woman patient might be outlined as constipation, laxative phenolphthalein eruption, excoriation, sulfonamide salve, sulfonamide sensitization, and sulfonamide-resin nail lacquer dermatitis enduring unrecognized, with attendant suffering, loss of time, medical expense and the likelihood of still further complication.

Dermatitis of the hands is seldom a simple thing etiologically and in the study of any case the person as a whole and his environment as a physicochemical and sociobiologic complex may have to be taken into account.

MANAGEMENT OF CHRONIC DERMATITIS OF THE HANDS.—When one sees, then, a case of dermatitis of the hands of obscure etiology, *in contrast to the cases* of easy interpretation and in contrast to cases of some recognizable traditional entity of unknown etiology such as psoriasis, the procedure that I utilize follows upon the attempt to answer the question, "What keeps this patient from getting well?" Is the skin repetitiously injured by chemicals it touches? Are parasites locally reproductive or are they continually fed into the region from foci of infection, so that the patient's lesions cannot heal? Is the patient's inability to mend due to nutritional or metabolic deficiency? Lowered resistance takes on added meaning when it is interpreted in the light of protein nutrition, liver function and endocrine harmony.

It is the physician's job to create the optimum circumstances which favor healing, and that is all he can do. "Chronic" dermatitis of the hands may be said, arbitrarily, to exist when disease has persisted for two months or more. Cases of such duration are, practically speaking, always due to a complex of etiologic factors. The following efforts, then, are appropriate and broadly inclusive.

1. See to it that no physical agencies or nervous hypermotility and excoriation interfere with healing. Instruct the patient regarding the need for quiet, rest, and relaxation. Help him to allay anxieties and practice amateur psychiatry if indicated. Do not withhold sedation.

Caffeine is a stimulant of the nervous system, and the skin is a peripheral ectodermal organ of sensation capable of being made irritable by the drug, as the central nervous system is. Caffeine interferes with sedation and rest. A given quantity of itching is less tolerable and more annoying when the patient is overstimulated. Caffeine is often used by a hypothyroid patient to mask his symptoms of hypothyroidism. Such persons are well served by the physician substituting the right dose of thyroid for the wrong dose of caffeine. Balancing the physiologic dose of thyroid is impossible when caffeine is being taken in excess. It is advisable for these reasons to restrict severely the ingestion of coffee, tea and the cola drinks by patients with chronic dermatitis.

2. See to it that no chemical likely to irritate the skin touches the hands. Allow contact only with water, cotton, linen, and carefully selected, rarely irritating medicines, such as aluminum acetate or boric acid, a teaspoonful to the quart of water for cool compresses, and petrolatum or phenolated zinc paste.

The elimination of contactant irritants can be accomplished by following a technic which is based on the fact that, although at first one does not know the cause one can probably eliminate it by eliminating everything that is likely to be causative (Sutton: JMoMA 44: 481, 1947 ADS 59: 86 1949) The skin heals of its contactant injury usually within a week or two of inconvenient living in chemical isolation o fails to heal if the elimination is not successful, in which case the eliminative effort must be intensified until exclusion of the unknown cause does succeed, even if this requires hospitalization. The the chemicals with which the patient desires to come i to contact are replaced upon his skin in an orderly fashion, one each day so that the flare whi h follows application of the irritant serves to identify it. During the period of isolation, the patient wa hes only with water and allays itching with cool water boric acid, or aluminum acetat compresses, along with petrolatum as a lubricant and sedation with ba biturates or chloral. Note the similarity of method in identifying contactants by single-item addition to that of identifying food allergens by the single-food additive diet (Winston and S tton: Pract 160: 347 1948) This technic can be used effectively See p. 159





Figs. 1093 and 1094 —Chronic dermatitis of the hand.

Patch testing, properly carried out and properly interpreted, yields valuable information and may speedily supply data which the use test described above would i some circumst nces yield only in relatively cumbersome way Ayres often perform preliminary patch tests with various medicines and ointment bases intended fo use on the patient i the course f treatment Pretreatme t pat h tests with therapeutic agent have been ad ocated by Goodman and Sulzberger (ADS 35 044, 1037) They may be done t the time of the pati nt s first visit. Even such seemi gly innocuou substances a hydrous wool fat, Vaseline, Aquapho and iodochlorhydroxyquinoline ointment may t times cause trouble and in som inst nces in which preliminary patch test have not been performed embarrassme t has followed. An appreciable number of cases of contact dermatitis occur in which activity of disease i maintained as a result f intol rance to simple o ntment bases.

3. Elimi ate coccic parasites as well as possible by using iodochlorhydroxyquinoline ream, 1 4,000 potassi m permanganate 2% queous methyl-rosaniline chloride gentle débridement % ammoniated mercury paste Achromycin r bacitracin oi tment, tetracycline admi istered by mouth or penicillin given by injection A mixture of % sulfur nd 0.6% mg f chloramphenicol in iodochlorhydroxyqui oli cream is a topical antiseptic with a wid range f ffectiveness against cuta eous pathogen of several kin l and a low index of sensitization. I have had little success with autogenous vacci es an l staphylococcus toxoid became largely outmoded when the antibiotics and Vioform proved so effective

4. Eliminate all focal infection with due attention to feet as sources of dermatophytids, teeth and gums, tonsils prostate, uterine cervix, and bladder Some consultants who hold a D.D.S. degree do not know oral infection when they stare at it, and some gynecologists fail to cure an erosion of the cervix or to achieve a shipshape cystocele repair This situation makes it necessary for the dermatologist to choose his consultants rather than to allow the patient freedom of selection in the matter

5 Promote optimum capacity to heal in the patient himself by insuring adequate nutrition with respect to both vitamins and protein. Give due consideration to liver function and to hormonal equilibrium.

6. Consider the advisability of investigating food allergy by single-food additive dieting but estimate this effort as quite unlikely to prove fruitful and as grasping at a straw Skin tests are seldom of value in seeking food allergies, despite their significance in theoretical and investigative medicine. Ayres employs scratch tests in selected cases in which the history and clinical appearance point to the possible diagnosis of atopic dermatitis. Although disappointments are frequent, occasionally valuable clues turn up.

7 Hold back on x ray therapy and use it conservatively by necessity rather than by whim. X ray therapy is necrobiotic, but it does not kill parasites. It has cumulative effects which can cause serious harm, harm which is especially serious when the hands are damaged, for they contain no skin to waste. Yet x ray therapy induces resolution of inflammation and so may have great value in palliation. It seems temporarily to achieve nonspecific desensitization of the skin, and it usually allays itching symptomatically inducing vesiculation to dry up. When x ray therapy is applied to a vesicular dermatitis and that dermatitis gets worse promptly bacterial cultures will probably show that *Micrococcus aureus* is at work, and one may surmise that antibiotics will achieve success. In lichen chronicus simplex one would be hard put to it to bring about a cure without x-ray therapy

X ray therapy obviously should be carried out only by one thoroughly qualified in this field yet radiologists have no business to be in charge of a case of dermatitis, for they simply do not know enough dermatology Dermatologists, on the other hand, are obliged to know enough radiology to use the tool correctly—as they must likewise be able to use a scalpel correctly—in the therapy of dermatoses. A dermatologist, furthermore, has to know enough about radiology and possess wisdom enough to stay out of trouble.

8. Other measures worthy of consideration include the use of cortisone, ACTH and hydrocortisone oi tment. These have great value especially in palliating cases of the chronic lichenoid type including pustular psoriasis and recalcitrant acrodermatitis, which interestingly was reported to have responded to quinacrine given orally by Cormia and Noon (ADS 68: 337 1953)

See Sutton (J 45 407, 1915), Cornbleet (IndustM 11: 55, 1942) Anderson (J 123 184, 1943) physicians' hands Madden, Nomland, Caro, Montgomery and Montgomery and Kutcher (J 124 743, ff., 1944) hands and feet Carpenter (JMSocNJ 42: 262, 1945) recurrent eczematous-pustular cases, cause and management, Blaisdell and Swartz (ADS 51 305, 1945), pompholyx Tobias (SouthMJ 39 336 1946) 200 cases of hand involvement, causes; Dysidrosis (JAllergy 19 333 1948), milkers eczema, Samitz (ADS 59: 146, 1949) multiple and interacting etiologic factors O'Leary (JKansMS 50 205, 1949) brief review) Guthrie and Mandel (ADS 63 454, 1951) lesions due to food allergy Gaul and Underwood (AmerPractit J 14, 1952), overtreatment Cormia (CanadMAJ 66 461, 1952), etiologic factors in 150 cases; Waldbott (GP 6 32, 1952) contact dermatitis patterns; Silverman and Littman (NEngDJ 249 639 1953) examination of hands in cardiovascular diagnosis, Edit (J 154 591, 1954) hands in internal medical diagnosis Engman (SouthMJ 47: 67, 1954), housewives' eczema, Gomez Orbaneja and Quinones Carva la (abs HJD 60 42, 1954) 10 types of dermatitis of hands in 330 cases, including 3 of palmar hyperkeratosis attributed to mycosis or contactants Brunner (J 154 894, 1954), housewives' eczema largely contactant, Gross et al. (ADS 70 94, 1954) impairment of alkali neutralizing power in nummular and housewives' eczema, correction by nutritional and systemic measures rather than control of contactants Fredricks and Becker (ADS 70 107, 1954), tension, anxiety nervous fatigue, dyshidrosis and secondary infection J lison and Piper (AD 71 438 1955), inhalant factors and hyposensitization; Jambor and Suskind (JID 24 379 1955) soaps and detergents innocent of sensitizing.

Dermatitis of the Ears—The skin covers the pinna and the external auditory canal the epidermis being continuous with the external covering of the tympanum. The work of the dermatologist and the otologist overlap in this region. Sebaceous cysts acneic nodules behind the ear or within the lobe painful nodule (q v) congenital auricular fistula (q v) accessory auricular appendages (q v) and gout are among the conditions to be met in this region. Carcinoma of the skin of the ear is in the large majority of cases of the squamous cell variety Cancer of the ceruminous glands (q v) is quite rare The auricular skin is subject to intertrigo impetiginization, furuncles, infectious eczematoid dermatitis erysipelas frostbite sunburn lupus erythematosus, dermatitis venenata, seborrheic dermatitis and lichen *chronicus simplex*, all described elsewhere See also Otomycosis (p 500)

When the skin of the external auditory canal is i flamed, management involves mechanical as well as diagnostic problems because of relative inaccessibility of the parts, which must be kept clean. The dermatologist and otologist may collaborate to the advan-

tage of the patient, for dermatologists are seldom able skillfully to remove débris from deep within the ear canal, and the otologist makes no claim to dermatologic competence. Dermatitis of the canal is of course a common complication of the chronic draining ear which is a problem of the otologist (Punt: BMJ 1: 989 1949).

Bacteriologic investigation is highly desirable in cases of chronic otitis externa, which are seldom mycotic in origin (see Otomycosis) While staphylococci, streptococci or both are frequent invaders, *Ps. aeruginosa* infection (q.v) is frequent in this location and difficult to eradicate. A diphtheroid was blamed in the case of Eller and Kest (ADS 41: 1020, 1940) In 100 cases studied bacteriologically by Salvin and Lewis (JBact 51: 495, 1946) Pseudomonas was found in 45, various diphtheroids in 14, *Strept viridans* in 9 and several other organisms with lower frequency of incidence. They used tincture of Merthiolate and sulfonamide powder the latte being disapproved by present-day tandards because of the hazards of sensitization but their recognition of the fact that otomycosis is exceptional was an important contribution. Morley (BMJ 1: 372, 1928) was among the first to call attention to the importance of *Ps. aeruginosa* in otitis externa. Cultures in 168 patients with 253 infected ears showed Pseudomonas in 104, staphylococci in 96, Gram positive bacilli in 26, streptococci in 10 Gram-negative cocci in 10 pneumococci in 4, monilia in 10 and saprophytic molds in 41 (Gill and Gill: SouthMJ 43: 428, 1950) The f equency of pathogenicity of *Ps. aeruginosa* was recognized by Syverton et al. (AOtol 43: 213 1946) and this organism can be attacked with probable success by means of streptomycin, Chloromycetin or neomycin in aqueous solution, the last being the prefer nce of Sulzberge and Baer (YBD 1951, p 10) who cautio ed against using it if perforation of the drum is present. Daily irrigation with thorough rinsing and aspiration was their recommendatio , using neomycin 5 mg. per cc. Finding *Ps. aeruginosa* a common pathogen Koe (JIowaMS 39: 560, 1949) recommended ear wicks saturated with bacitracin o tyrothrycin; dequate cleansing is a requisite. Ochs (J 142: 1361, 1950) attacked the organism with 2% acetic acid douches and tampons the effectiveness of which agent was demonstrated by Owen (JBact 52: 353, 1946) Chloromycetin, 10 mg per Gm. in Carbowax, a water-soluble base often helps (Cornbleet and Schorr: ADS 62: 907 1950) I frequently combin sulfur 2% and Chloromycetin 0.6% in 3% Vioform Cream with good effect. Polymyxin was the antibiotic of choice of Graves (EENTMonthly 31: 33, 1952) One pe cent iodine is a good antiseptic, believed Story (BMJ 2: 1123 1952) Hydrocortisone suspension, combined with an antibiotic when indicated, was highly recommended by Bae and Litt (J 155: 973, 1954) Neocortef deserves its popularity here.

In dealing with chronic dermatitis of the ears, one must take into consideration the heterogeny of possible causes, as in chronic dermatitis of the hands (q v) Combinations of etiologic factors require recognition and individualized therapy (McLaurin J 154 207 1954) Contactants which frequently interfere with healing of the inflamed ear include cosmetic articles applied to the hair and scalp, nail lacquer soap and medicines themselves. Parasites acting locally were discussed earlier focal infection is likewise important, the teeth, tonsils and paranasal sinuses being frequent offenders. The same problems of nutritional and metabolic dysfunction apply to dermatitis of the ears as to dermatitis of the hands. Seborrheic dermatitis of the scalp when present, must be eliminated. Dermatoses of unknown cause such as psoriasis and lupus erythematosus, when they affect the external ear are treated in this location as they are elsewhere on the skin.

A furuncle in the ear canal is exquisitely painful. It may be expected to respond to antibiotics and x ray therapy while pain is allayed with ice bag or hot pad, whichever feels better to the patient, and narcotics in adequate dosage Recurrent furunculosis of the ear region may yield to Terramycin ointment x ray therapy elimination of contactants and focal infections, and appropriate attention to nutritional and hormonal balance. Acne, perhaps requiring thyroid and estrogenic hormones for its correction, is among the diseases to which recurrent, seemingly coccic pustules in the ear may be due

An inherited syndrome of draining ears, eczematoid dermatitis of the face and bloody diarrhea was apparently disclosed by st dies of a case with these features which proved fatal in a little boy (Aldrich et al.: Pediat 13: 133, 1954)

Pustular Perichondritis of the Ears, described by Lehmann and Pipkin (SouthMJ 32 874 1939) follows trauma, affects boxers fo example is characterized by purulent inflammation that dissects the perichondrium, and results in gross disfigurement. A bloody effusion beneath the perichondrium is likely to be the starting point, occasioned perhaps by traumatization of a sea already present. The treatment prior to the introduction of the antibiotics included incision and drainage (Howard Laryngoscope 15: 81, 1935)

Leg Ulcers comprise a variety of chronic dermatitis with tissue loss. As Luke (CanadMAJ 43 217 1940) wrote there is a tendency to devote too much time on local treatment and too little consideration to etiology. The article of Callaway et al. (SouthMJ 39 375 1946) deserves careful study. Leg ulcers are often associated with lichen chronicus simplex (q v) a disease in which nutritional imbalance especially hypoproteinemia, is usual, if not primarily causative. In addition to efforts directed at such dermatitis, and at tinea of the feet, if present (Marshall MTimes 75 154, 1947) one has also a problem in tissue culture, *for the ulcerous defect must be filled with granulation tissue and re-covered with epithelium*.

Adequacy of nutrition of the tissues of the legs is concerned with factors affecting (1) the tissues external to the vessels, (2) the tissues of the vessels themselves, and (3) the circulatory tissue—the blood itself—within the vessels. Cicatricial tissue about the vessels, following trauma or chronic dermatitis, may be the major factor interfering with nutrition of the deeper and distal structures of the leg. Obliterative vascular disease interferes with nutrition of the extremity. Circulatory defects of cardiac origin are capable of producing defective nutrition of acral tissues which occurs in decompensation and high blood pressure. The blood may be inadequate to nourish the distal tissues properly because of anemia or hypoproteinemia resulting from a wide variety *of causes* but *particularly from malnutrition*. In undertaking to obtain optimum acral tissue nutrition, each group of possible causes, extravascular vascular and endovascular should be considered systematically individually and collectively.

The etiologic factors, in the order of the frequency of their influence in 847 cases of ulcers of the legs, were pregnancy occupation injury febrile disease with phlebitis, and heredity reported Smith (PSMMC 9 193 1934). The causes of venous stasis include (1) pregnancy childbirth, trauma, which may be surgical, infection or immobilization resulting in thrombosis; (2) varicosity with defective valves; (3) external pressure from, for example an abdominal tumor; and (4) lack of muscular contraction, such as may occur in paral is (Anning BMJ 458, 1949 1205 1950). While inheritance of varicosity is significant, it does not necessarily result in thrombosis followed by ulceration. The chief cause of leg ulcer is chronic venous insufficiency brought about by thrombosis of deep veins the prevention of which is paramount if leg ulcers are to be prevented (Anning Lancet 759 195_)

The hydrostatic mechanics of chronic venous insufficiency was studied by Farber and Batts (AIDS 70 653 1954) who explained that increased capillary pressure results in rupture of capillaries and so in pigmentary changes, while lymphatic damage results in lymphedema, cutaneous sclerosis follows cellulitis and lymphangitis, and sluggish ulcers *develop in the progressively more defective dermis and subdermal tissues.*

Inadequacy of venous valves is a heritable malformation, so that varicosity is a familial disease. In 50% of 334 cases of leg ulcer reported by Jensen (AnnSurg 95: 735 1932) the disease was familial, and this was true of half of the 1,000 cases of Payne (BMJ 1 857 1936) who noted a 4 to 1 preference of varicose ulcers for females. The absence of valves in the external iliac and femoral veins, unilaterally or bilaterally was demonstrated by Eger and Casper (J 123 148 1943). Such congenital absences causing varicosity were dissected by Curtis and Helm (AIDS 55 639 1947). Back pressure in the vein due to defective valves results in transudation of lymph fibroblastic proliferation and circumferential scarring, explained Homans (SGO 4 300 1917 BostonM&SJ 193: 379 1925) and he recommended the excision of the band scar. Infrared photography revealed inflammation of the vein which appeared to extend outward so as to produce dermatitis, so that eventual ulceration was attributed to inflammatory disease rather than to mere chronic passive congestion by Zimmerman (AIDS 34: 97 1936).

Surgeons tend to attribute too large a share of causation of leg ulcers to stasis. Most dermatologists are incompetent to *estimate or treat* the circulatory aspect of the disease and require surgical and medical consultants. In general the venous return from the legs follows 2 courses: veins external to the deep fascia overlying the muscles and veins internal to this fascia. When only the external veins are defective, a pressure bandage is helpful and comfortable and the external veins may be occluded or removed to the advantage of the patient. When the deep veins are inadequate a pressure bandage is intolerable and occlusion of the only remaining veins would be disastrous.

The selection of candidates for vein surgery was clarified by Pratt (J 122 797 1943); see also Ochsner and Mahorner (Varicose Veins, Mosby 1939) and Allen et al. (Peripheral Vascular Diseases, Saunders, 1946 p. 666 ff.) Arterial supply is estimated by the history regarding claudication, the skin temperature and appearance, and the palpation of pulses. The deep veins may have been occluded by milk leg. Their patency may be determined by emptying the veins by elevation, measuring the thigh, calf and ankle applying a pressure bandage, and allowing the patient to walk for 10 minutes. On remeasurement the circumferential measurements should decrease if the deep veins are open but the volume of the extremity will increase if they are not, and the bandage will probably cause pain. The saphenous-femoral vein is tested by elevating the extremity applying a tourniquet high in the groin, then placing the patient upright to remove the tourniquet and to note whether the veins fill from above or below. Rapid filling of the veins from above indicates valve failure. Incompetence of communicating branches is determined by applying the pressure bandage from the toes to the groin and placing a tourniquet proximal to it. As the bandage is removed, sudden protrusions of collection of veins show the point of incompetence and these veins are marked for subsequent resection.

Ateriosclerosis obliterans as a cause of leg ulcer was discussed by Shapiro and Nomland (ADS 61 80 1950) who noted that the typical patient is an old man showing thin, shiny atrophic skin thick dystrophic nails mottled redness of the feet on dependency and pallor on elevation with slow return of redness after the leg is lowered. Temperature changes are likely to be present, intermittent claudication is a complaint, and x ray may reveal calcification of the arteries. Usually lacking are varicosities, history of thrombophlebitis, chronic cellulitis, edema and hemosiderin deposition.

Leg ulcers in association with various blood dyscrasias, including Mediterranean anemia and polycythemia were noted by Pascher and Keen (ADS 66 478 1952)

Leg ulcers occur in sickle-cell anemia, a familial disease (Woofter AIntM 76: 230, 1943); but the lesions as such are not distinctive. They were chronic and bilateral, resembling syphilitic gummas but unresponsive to treatment in the patient of Cummer and LaRocco (ADS 42 1015 1940) A leg ulcer associated with sickle-cell anemia was helped by liver therapy given by Schwartz (ADS 37: 866 1938) Such a lesion healed during pregnancy in the case of Cornbleet (J 148: 1025 1952)

Leg ulcers associated with congenital hemolytic jaundice have been cured by transfusion and splenectomy (Taylor: J 112: 1574, 1939; Lege and Orr: SouthMJ 33 463, 1940)

Chronic leg ulcer occurring in diseases of the blood was the subject of a review by Gendel (Blood 3: 1283, 1948) who discussed the association in congenital hemolytic anemia, sickle-cell anemia, polycythemia, splenic anemia, thrombocytopenic purpura and Gaucher disease. An early report of association with thrombocytopenic purpura was that of Witt (BMJ 1: 809 194_) Nonthrombocytopenic purpura was the cause in 3 cases of ulcers about the ankle observed by Hoyle and Truelove (BMJ 1 633 1955)

Idiopathic familial dysproteinemia was reported in several members of a family by Homburger and Petermann (Blood 4: 1085, 1949) Hypoproteinemia was accompanied in the adult patients with peripheral vascular changes, edema and, in the males, ulcers of the legs. While edema and leg ulcers were the presenting features yet the diminution of blood protein was less than that usually required to produce edema. Other congenital malformations were present, including defective development of the thoracic cage and peculiarity of distribution of the hair of the occipital region.

Cases of Felty's syndrome, suffering from arthritis and a form of hypersplenism manifested by leukopenia, are afflicted sometimes with leg ulcers (Schoch: ADS 66: 334 195_)

TREATMENT.—In general, a leg ulcer should be treated in such a way as best to enable tissue growth to occur (Reid: AnnSurg 105 982, 1937) Then what is put onto the ulcer itself is a matter of indifference so long as it is not injurious, and cod liver oil chlorophyll, red blood cells, pectin, silver foil insulin maggot juice merely zinc oxide ointment or petrolatum are equally satisfactory. When a topical agent seems to accelerate wound healing it does so by the prevention of or reduction of factors which tend to retard healing (Sulzberger and Baer YBD 1944, p 449)

Supportive bandaging or an Unna paste boot is helpful (Fillmore: TexasSJM 35 91 1939; Zimmerman and Faller: SGO 70: 792, 1940; Isaacs: ADS 41: 530, 1940 Marbury and Jackson: VAMMonth 67: 283, 1940; Gordon: CanadMAJ 4_: 4, 1940) Supportive

strapping with strips of adhesive tape applied transversely not completely surrounding the limb *from* below upward, so as to cover the ulcer and to splint the whole inflammatory region, is a time-honored and effective method of treatment, dating back to the 1799 publication in London of Thomas Baynton (see Gilje: ActaD-V 28 454, 1948) Elastic adhesive (Elastoplast) similarly laid on, was recommended by Lain (JOklaMA 26: 1[illegible], 1933) Douglas (SGO 61: 458, 1935) and others. Massage and movement were combined with a careful technic of padding and bandaging in the management of stasis dermatitis and ulcers by Bisgaard (rev BMJ 1 107 1950)

Vitamin intake and requirements must be considered (Maynard and Hollinger J 121 1194 1943) Nutritional eczema was clarified by the essay of Guy et al. (ADS 57 822, 1948) whose old patients with chronic sore legs and bad teeth were markedly improved by hospitalization, high protein diet, and dental repair work which included the construction of prostheses so that the patient could nourish himself properly

Treatment appropriate for peripheral vascular disease when it exists, may prove beneficial. Thus paravertebral sympathetic ganglion block was beneficial in a number of patients so treated by Naide (ADS 57 655 1948) The presence of dermatitis of the leg may cause reflex vasoconstriction such that its relief by this means is followed by improved nutrition of the part.

Plastic surgery utilizing full thickness grafts after excision of the entirety of the diseased tissue offers great advantages both as to rapidity of cure and excellence of results, when the method is applicable which of course it could not be if the cause were obliterative arterial disease (Greeley Geriatrics 8 527 1953) Penicillin by injection before and after grafting improves the likelihood of takes (Nomland and Wallace J 130 563 1946)

ACTH and cortisone have proved successful in enabling patients with sickle-cell anemia to heal (Sass NEngJM 246 583 1952 Rice ADS 68 576 1953)

See Carrel and Hartman (JExperM 24 429 1916) rate of repair as mathematical function of area (cf. DuNoüy ib 24 461, 1916) giving by formula the normal time for wounds to heal (I think unreliable); Brunsting and Simonsen (J 101: 1937 1933) cysteine 0.5% in saline to supply —SH stimulus Sutton (J 104 2168, 1935) thioglycerol; Robinson (AmJSurg 33 192, 1936) urea; Greenbaum (AmJSurg 34, 259 1936) allantoin, Ayres et al (ADS 33, 31, 1936) maggot therapy, bibliography Kaplan (J 108 968, 1937) allantoin Wise and Sulzberger (YBD 1937 p. 415) oil or foil; Lohr and Unger (ArKlinChir 189 405, 1937) cod-liver oil ointment Epstein (AmJSurg 36 472, 1937) cod-liver oil no good; Orr (SouthwestM 22 354, 1938) wound healing, Robinson (AmJSurg 47 111, 1940), ammonium bicarbonate in maggot secretion Gurd and McKim (AmJSurg 51 584, 1941) BIPP bismuth iodoform petrolatum paste Tompkins (SGO 72: 222, 1941), pectin Giordano (SemMed 49 928, 1942) tape glass plat over ulcer Hoehringer (abs J 121 793, 1943) chlorophyll ointment Gahan (ADS 47 849, 1943) chlorophyll, Naide (AmJMedSci 206: 489, 1943) autoblood concentrate application, Murray and Shaar (J 125: 779 1944) blood cell paste and powder Edit (J 128 290, 1945) chromosomal material stimulating wound healing Irvine (BMJ 1 120 1946) plaster cast Anderson et al (AmHeartJ 32 754, 1946) powdered red cells Reif (ADS 54 407 1946) oil or foil (quoted Isaak DWchn 93 607 1931); Col (AmJSurg 76 38, 1948) placental blood and extract Byars and Letterman (SGO 89 583 1949) split-thickness grafts Bird (SouthMJ 44 601, 1951) hyaluronidase for moist compress helpful; Madden and Ra[illegible] (J 149 1016, 1952) débridement and benefit with streptokinase and streptodornase and trypsin Black (BritJCanc 6 120, 1952) 4 carcinoma and 2 sarcoma cases developing in old leg ulcers, 72 in literature Döring (DWchn 127 596, 1952) excision and grafting in 24 resistant cases treated by plastic surgery Hellesen (JID 22 7 1954), rapid débridement with crystalline trypsin applied for 4 to 6 hours daily Chernoff et al. (J 155 1487 1954), 6 leg ulcers in sickle-cell anemia healed fast on bed rest, local therapy and maintenance of RBC and Hb levels; Hilberg and Tolmach (J 155 1219 1954) Gelfoam powder therapy Anning (Leg Ulcers Their Causes and Treatment, Little, Brown & Co 1954) monographic, personal and clear Robinson (J 157 27, 1955) antibiotic powder therapy in stasis ulcers Reisch and Combes (J 157 36, 1955) tailored canvas pressure bandage with foam rubber; *Gasser* and Costello (J 158 131 1955) sponge rubber boot.

Tropical Ulcer.—Many synonyms exist, including Desert Sore Veldt Sore and Barcoo Rot. The extremities especially the legs, particularly if these parts are unprotected by clothing are the usual location. A minor trauma or insect bite is the initial lesion, and there quickly develops a tense or flaccid bulla, its content at first clear or sanguineous, later purulent. Exactly beneath the bulla the dermis undergoes necrosis, so that a painful, punched-out ulcer develops. This enlarges slowly and remains a chronic and rebellious sore, in which bacteriologic investigation reveals variously Vincent's organisms, staphylococci, streptococci, and sometimes *C diphtheriae* The lesions may become large and deep, even exposing bone They are solitary or few in number

In classic cases I have cultivated from initial blebs only hemolytic *Staphylococcus aureus* and have thought the sloughs due to its dermonecrotizing toxin. Experimental inoculation of a human being with a staphylococcus obtained from beneath an undermined epithelium resulted in a take reported Harman (JPath 9: 1 1904) who recognized that in treatment ointment preparations were not effective but good food, débridement and bichloride of mercury soaks resulted in cure Cultures from cases seen in Arabia yielded *Staphylococcus aureus* reported Martin (BMJ 1 761, 1917) A spirochete was found in one-third of his patients, from whose sores *staphylococci* and streptococci were

also cultured, by Corpus (J 82: 1192, 1924) in confirmation of Halpin (USNMB 12: 80, 1918) explaining the usefulness of injections of arsphenamine, the spirochetieidal drug then available. Diet, dirt and staphylococci were the etiologic factors in Australian troops observed by Butler (BMJ 2 731 1943) (Bettley JRoyArmyMC 81 107 1943.) Difficult cases had t be mo ed to a temperate climate before they would get well (Devine: MJ Austral : 761 1943) Cultures from early lesions disclosed a Gram-negative coccobacillary organism named *Micrococcus mycetoides* by Castellani (abs BJD 60 424 1948) in cases he described as tropicaloid ulcers, wherein the painless, shallow sores had margins that were ot raised or undermined; see Castellani (JTropM 51 45, 1948) Poindexter (ADS 62: 624, 1950) reporting various bacteriologic findings in Liberian cases, thought therapy more effective when the specific flora had been determined.



Figs. 1093 and 1094.—Tropical ulcers. (Dr O. G. Costa.)

A thorities have ascribed tropical ulcer in part to humidity or to dryness, depending on where they h ve seen their cases. It is a hot-climate or summ rtime disease as a rule Patients often but not always, are ill-nouri hed, malarial, or otherwise below par Blood personnel may be more suscept ble than the dark-skinned natives (Henderson BMJ 1: 657 1943)

If the earliest lesions are promptly and caref lly attended, using gentle débridement, cleansi g, and tiseptic, such as gentian violet, ulceration is prevented (Vischer: abs YBD 1943, p 303) After ulceration, there h ve been recommended permanganate com presses, clea liness, occlusive dressings, sulfonamides and intravenous arsen xide. In the later stages of the disease rest, levation, splinting a d adequate nutrition were recommended by An ing (TransRoySocTropM 40: 313, 1946) Relatively speedy cures were obt ined by Obrien (BMJ : 1844, 1951; EAf MJ 29: 453, 1951) in African cases by using penicillin and occlusive supportive dressings followed by skin grafts.

See Brown (JTropM 38: 157, 170, 187, 1935) dietary inadequacy and the tropical ulcer syndrome; Gunther (MJAustral 1: 340, 1936) Vincent's organisms; Hamberger (IndMGaz 74: 151, 1939) "frontier sore," various bacteria in 33 cases, Vigors (JTropM 44: 33, 1941) toes involved; Rapport (BMJ 2: 96, 1942) 1,000 cases; Charters (TransRoySocTropM 37: 205, 1943) avitaminosis A in 135 East Africa cases, Bharucha (IndMGaz 78: 532, 1943) nonspecific etiology, Gill (ADS 49: 408, 1944), *C diphtheriae*, Feinman (NEngJM 231: 575, 1944) Vincent organisms, Costa (ADS 49: 260, 1944) Vincent's in some, cocci in others, Webb (BMJ 2: 49, 1946) Vincent in South China cases, cured with penicillin, Golden (SouthMJ 40: 214, 1947) thickening of vessel walls in Central American cases, Blank (AmJTropM 27: 383, 1947) Vincent' ulcer, Hare (JTropM 51: 99, 1948) vector must be crawler a tick or mite, Assam cases

See also ecthyma, diphtheria, leishmaniasis, gangrene due to infection, "jungle rot.

Balanitis.—Dermatitis of the foreskin and glans is often contactant due to soap, medication rubber contraceptives used by the partner sometimes garments. Infectious gangrene (q v) may affect this region. Lesions to be considered include those due to lichen planus, lichen sclerosus, psoriasis, lymphopathia venerea, gonorrhea, Vincent's disease, chancroid, syphilis, scabies and malignant erythroplakia (q.v.)

An intertriginous balanitis simulating erythroplakia is occasionally seen, curable only by circumcision. The thin, bright red, glistening, slightly exudative lesion has a fairly sharp margin. It is unresponsive to topical medication (Zoon Dermatologica 105: 1 1952)



Fig. 1097.—Balanitis of the sort that only circumcision cures

See Madden (J 105: 420, 1935) varieties of balanitis, Carlson (JAMA 34: 147, 1937) destructive genital lesions, Morris (ADS 54: 610, 1946), erythroplakia-like intertrigo, case Becker and Obermayer (Modern Dermatology and Syphilology Lippincott, 1940, p. 88)

SCALY DERMATOSES OF UNDETERMINED CAUSE

PITYRIASIS ROSEA

Symptoms.—Pityriasis rosea (Herpes tonsurans maculosus of Hebra) is an acute inflammatory dermatosis characterized by a self limited eruption of numerous yellowish pinkish or reddish scaly macules of various sizes and shapes asymmetrically distributed over the trunk and limbs. As a rule constitutional symptoms are entirely wanting. An initial large single plaque likely to be located somewhere on the trunk usually precedes the general outbreak by 1 or 2 weeks. The lesions develop as oval macules of irregular outline or slightly edematous maculopapules from 0.5 to 5 cm in diameter thinly covered with soft white thin, branny scales. These loosen centrally and peel centrifugally their attachment being inside the mildly erythematous and edematous border of the lesion. A typical lesion, oval and of fingernail size exhibits a central, round collarette of scales, the normal presence of which may be obscured by friction or medication. The long axis of a lesion parallels the lines of cleavage of the skin. The border is somewhat irregular not definitively sharp. The patches may increase slightly in size and the central portions tend to clear giving rise to slightly elevated reddish rings with fawn-colored centers. The eruption may be limited to the trunk but the upper arms and the thighs frequently are attacked. Rarely is the face involved. Symptoms are mild although itching may be present especially when the patient perspires and in severe cases. The eruption disappears spontaneously in a few weeks. Most cases cleared in from 2.5 to 4.5 weeks, a number lasted 6.5 weeks, and a few persisted 8.5 to even 14 weeks in a series of 221 cases statistically studied by Crissey (JID 23: 85, 1954) who found the duration uninfluenced by antihistamine treatment. Recurrences are rare but are recog

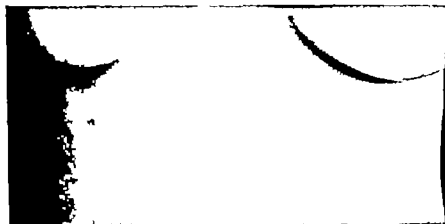


Fig. 1098.—Pityriasis rosea, herald patch on epigastrium. (Dr Clyde Cummer)

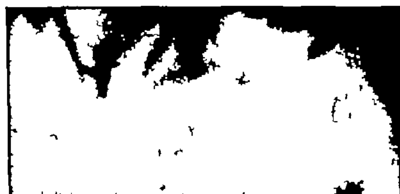


Fig 1099.—Pityriasis rosea, early lesions.



Fig. 1100—Pityriasis rosea. (Dr J Lamar Calloway)

nized (Sayer BJD 46 181 1934 Engman and Kile ADS 34 272, 1936) The duration of an attack seldom exceeds 2 months (Niles and Klump ADS 41 265 1940)

Unusual and anomalous variants occur They were classed by Klauder (J 82 178 1924) in macular urticarial, papular and vesicular forms

Macular	Punctate, Guttate, Nummular, Circinate	Bilateral, Unilateral, Generalized, Localized	
		Confluent, Diffuse	Pityriasis rosea gigantea (Darier); Pityriasis circiné et marginé (Vidal)
Urticarial	Pityriasis rosea urticata (Vörner); Urticée pityriasis rosea (Hallopeau)		
Papular	Maculopapular, Follicular		
	Miliary	Large, Small	
Vesicular	Pityriasis rosea with vesiculation		



Fig 1101 —Pityriasis rosea.

Involvement of the scalp face, neck, forearms and legs is not really rare according to Davis and Waldriff (ADS 63: 376 1951) Purpura was seen in the lesions of the lower extremities in the unusual case of Hartman (ADS 50: 201, 1944) Oral involvement occurs occasionally in the form of ruffled desquamation or tiny erosions (Guequierre and Wright ADS 43: 1000 1941 Greenbaum ADS 44 55, 1941 Rosenbaum ADS 63 376, 1951) When fever accompanies the disease oral lesions are likely to be found (Costello ADS 53: 73, 1946) Axillary vesiculation generally is present in extremely severe cases *Harthausen (BJD 39 121 1927)* believed that in children the *scalp is almost* invariably affected. Greenhouse and Cornell (ADS 28: 828, 1933) recorded in a Russian 62 years old a gigantic herald plaque and unusual manifestations. Haldin Davis (BJD 45 71, 1933) and Bailey (ADS 32: 104, 1935) have reported involvement of the palms. Rusters (CeskAD 15 193 1934) observed pigmentation following an attack, a rare complication except in Negro patients.

Limitation of the eruption to the bathing trunk area was remarked by Costello *(ADS 38: 75 1938) the remainder of the body having been exposed* to the sun's rays; I have seen such cases. Where the skin is deeply tanned, the eruption does not develop (Kinnear BJD 60 200 1948) Herald plaques involving the penis were seen by Shelow (ADS 32 106, 1935) Circinate lesions apparently are commoner in Japan than here (Arase ActaD-V 30: 116 1937)

The article of P elval (BJD 44 231, 1932) is valuable for its clinical description and bibliography

Prodromal *malaise mentioned in classic descriptions*, is not noted commonly in my practice, but was said to have occurred in 36 of 85 cases of Gourvitch (*AnndeD 7: 466*, 1936), who obtained posit ve reactions with a streptococcus vaccine in 50 of 55 patients tested intradermally

Etiology—The cause is unknown (Photinos DZtschr 68 187 1934) If the disease is infectious, it is feebly so It appears to be due to some sort of parasitism despite the absence of a demonstrable specific agent It is a respectable disease of otherwise healthy young adults not ringworm, venereal disease, or transmissible infection—this brief and not completely exact statement is worth making to the patient who generally is alarmed if not itchy at the time he seeks medical care While 3 cases occurred in one household as reported by Shelton (ADS 59 115 1949) the explanation appeared to lie in statistical probability rather than cross-infection.

The age incidence is highest between 10 and 30 years, and the seasonal incidence is highest in the fall and spring months (Weiss et al. ADS 15 304 1927) The location of the primary plaque occurred most often on the anterior thoracic wall (30%) in the extended series of cases of Niles and Klump The onset often coincides with the wearing of a new garment (Epstein UCut Rev 47 61 1943)

Efforts to inoculate the disease by means of blister fluid obtained from the site of the herald plaque or with scrapings did not succeed (Wile ADS 16 165 1927) Reports etiologically incriminating microorganisms, such as *Saccharomyces hominis* productive of pityriasis rosea as a dermatophytid (Benedek UCutRev 35: 218 1931; ActaD V 17 151 1936) or *Cryptococcus duboism* (Gougerot BsocfrançD 44: 1708 1937) are given little credence.

Pathology—The papillary vessels are dilated and there is mild inflammatory infiltration consisting of many lymphocytes and a few plasma cells and mast cells. Slight intercellular and intracellular edema is seen in the rete here and there almost forming minute vesicles. The corneum becomes ribboned and detached. The reaction in many respects approaches that of a low grade eczematous reaction of the flexural infective type, and as such can be classed, both from the clinical and histopathological standpoint, as an eczematide stated Percival et al. (Histopathology of the Skin, Livingstone, 1947 p 85)

Diagnosis.—The disorder is to be differentiated from dermatitis medicamentosa, seborrheic dermatitis, tinea corporis squamous and circinate secondary syphilids and acute psoriasis.

Dermatitis medicamentosa (q v) may take the form of pityriasis rosea arsenicals and gold especially may evoke this phenomenon. Seborrheic dermatitis develops more slowly the scales are greasy, and the sternal and axillary regions seldom escape. Tinea corporis usually begins on some exposed part the lesions are seldom numerous, they develop slowly and fungi are demonstrable Papulosquamous and circinate syphilids are infiltered, give rise to pigmentation and atrophy and frequently involve the palms concomitant signs of syphilis, including a positive serum reaction, are present. In psoriasis, the infiltration and scaling are more marked, the elbows and knees seldom escape, bleeding points are to be found and the disease persists.

Treatment.—The eruption will disappear spontaneously within a few weeks. Scratchy garments, soap and fungicidal medication intensify the discomfort of the patient. Hydrocortisone acetate ointment sometimes works wonders, not always. A mild antipruritic agent may be comforting:

R	Phe ol	0.5
	Zinc oxide ointment	
	Ammoniated mercury ointment, 5%	aa 5.0
	Lanolin	15.0
	Limewater	to 30.0

Sig: Apply for relief of itching.

A few erythema doses of ultraviolet irradiation are likely to be curative. Sulfur preparations are irritating and valueless. Cool baths in 1:15 000 HgCl with suitable precautions, may be used successfully (Sutton SouthMJ 35 697 1942) A single intramuscular injection of typhoid vaccine was recommended by Ebert and Otsuka (J 123 1036 1943) Vass (ADS 51 203 1945;

58 231 1948) obtained cures by the use of trichophytin 1 500 intradermally starch baths and loose clothing to the last rather than to effects of the antigen Carpenter (ADS 52 184 1945) attributed Vaas's results. Spirocheticides were alleged to be promptly curative by Hollstrom (ActaD-V 28 325 1948) I watched a young woman die of acute yellow atrophy after having been given neoarsphenamine by a physician who interpreted her rash as a secondary syphilid.

PITYRIASIS SIMPLEX FACIEI

This disorder is characterized by patchy superficial, asymptomatic, dry scaling with partial depigmentation occurring by predilection on the faces of children. It may produce conspicuous unsightliness in a brunet or Negro and it may be almost imperceptible in a blond. It is not limited exclusively to facial distribution. Called by an ancient name dartre volante by Brand and Tas (Dermatologica 105 145 1952) it seemed to them to occur with greater prevalence among poor children and among males in Israeli, and they thought it to be associated with uncleanliness. I see these cases equally among the cleanly and uncleanly and among the poor and the well to-do The patches are not sharply demarcated. They show the fluorescence in Wood's light only of mild, uneven hyperkeratosis. Cultures for bacteria and for fungi yield ordinarily only a nonhemolytic micrococcus. When pale areas of pityriasis were sunburned and the surrounding skin was not, I mistook the disease on first glance for discoid lupus erythematosus in a boy I saw in 1954.

Topical medication generally seems to be without avail I have tried a wide assortment. *Hydrocortisone ointment seems helpful.* The disease is a persistent one apparently not due to a known parasite and it occurs in individuals of otherwise unexceptionable health. It is neither contact dermatitis nor pityriasis streptogenique (q v) It may eventually dissipate spontaneously I have thought ultraviolet light therapy helpful and associate the disease with pityriasis rosea which is often quite atypical in little children. A bland protective ointment such as Lassar's with mineral oil added to soften it, may be prescribed, and excessive soap is harmful. Schmidt (DWchn 126 1128 1952) reported several instances in which the disorder disappeared after removal of tonsils or adenoids.

Summertime Pityriasis of the Elbows and Knees.—A minor disorder of children that I see fairly often in the late summer appears over the elbows and knees in the form of superficial dry itchy partially depigmenting, irregular patches, only slightly infiltrated, harsh to the touch similar to atopic dermatitis but never flexural in location. The elementary lesion would seem to be papules 1 or 2 mm. in diameter so fine t so a to give homogeneity to the central region of the affected area and scattered peripherally in a concentration that diminishes rapidly as it recedes from the center The patient is always a child, the age range in my experience having been from 4 to 1 years. The lesions are not wholly confined to the elbows and knees but occasionally occur discretely scattered in greater or lesser profusion over the chest and back. *Depigmentation is partial,* resembling that of pseudoachromia parasitica but fungi are absent. Response is immediate to a few x ray treatments of 100 r along with 1% hydrocortisone ointment. Recurrences may be expected seasonally I have not been able to detect a contactant cause, if such exists. The etiology obscure The patients have been healthy otherwise. I have not seen elsewhere a description of this condition.

LICHEN PLANUS

Symptoms—Lichen planus is an inflammatory dermatosis characterized by an eruption of *small glistening violaceous* papules which are discrete but may coalesce to form rough scaly patches. The disease may be acute subacute or chronic In the acute form the outbreak which is sudden, is accompanied by some malaise The eruption may be general but is usually limited to certain regions. The papules are small and flat with plane or slightly indented tops and angular bases. The surface of the papule may be marked by striae (Wickham's striae AnndeD June 1895) or grayish puncta, and the lesion is often capped by a thin scale In color the violaceous papules range from pale to bright red. As a rule but not always, they are intensely itchy

A line of papules along a scratch is frequently seen. The acute form may merge into the chronic, or an acute attack may supervene on the chronic. In the chronic type, the disease usually begins insidiously The sites of predilection are the flexural surfaces of the wrists and forearms, the inner aspects of the knees and thighs, and the region of the lumbar spine. The face and



Fig. 1102.—Lichen planus shiny angulated, violaceous itchy papules in a typical location.

Fig. 1103.—Generalized lichen planus. (Drs. Fordyce and MacKee.)

scalp generally escape The eruption is symmetric as a rule On departing the lesions are likely to leave temporarily pigmented spots, sometimes slightly atrophic scars, particularly if they have been of long standing.

Localized and generalized types of the disease were distinguished by Tompkins (AD 71: 515 1955) who observed in the majority of his patients

initial localization, preceding by at least a week the appearance of distant lesions. Many cases remained localized Tompkins noted, and these were more chronic than the generalized cases and were likely to involve the limbs The duration of the disease was not influenced in his series by bismuth or x ray therapy averaging 8 months in the generalized form, 3 years or more in the localized.




Figs. 1104 and 1105.—Lichen planus, with annular lesions.

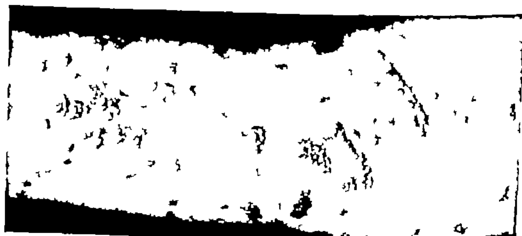


Fig. 1106.—Lichen planus in eruptive phase with linear lesions at sites of excoriations.

Mucosal lesions, which may precede the cutaneous, were recognized as being not rare by Crocker (MonatshPrakD 1 161, 1882) On the buccal mucosa, less often on the tongue the eruption occurs as sharply defined, whitish, lacy patches or streaks. On the glans penis it may take this form, although the papules are more likely to be of the cutaneous sort in size and contour Occasionally the mucous membranes alone are involved. Lichen planus affects other mucosae, occurring in the stomach, where the lesions resemble those seen in the mouth (Milian and Perin BsocfrançD 43 644 1936 Chevallier and Moutier MWelt 10 320 1936) and in the bladder (Young JUrol 43 265 1940)

A case in which the lesions were located only on the tonsils was seen by Thompson (BJD 40 91 1928) and a series of 10 cases confined to the mouth was reported by Fox (ADS 24 1071, 1931) Oral involvement in identical twins was seen by Epstein (ADS 45 382 1942)

Cheilitis in lichen planus may consist of lesions like those of the skin, or of the mucosae; it may even occur as an extensive inflammation with heavy purulent discharge (Montgomery ADS 38 401, 1938)

Involvement of the vulva is common, and in this location the lesions are quite similar to those occurring in the mouth. Here the disease is apparently quite confusing clinically as judged by essays in surgical journals. An occasional hypertrophic verrucose lesion, such as that of Knierer (DZtschr 75 279 1937) may resemble the papular syphilid Vulvar cases are frequently



Fig 1107—Acute lichen planus, unusually severe. (Dr J Lamar Calloway)

complicated by medicinal irritation, as well as by mycotic or trichomonad vulvovaginitis. Leukoplakia of neoplastic nature kraurosis (q v) and lichen planus, whitish and soggy where it is continually moist, are different diseases, with a different prognosis and treatment for each. See Hunt (BJD 48: 53 1936)

Involvement of the eyelids and conjunctivae was remarked by Michelson and Laymon (ADS 37 27 1938) Papules, plaques, and lesions like erythema ab igne occur on the skin of the eyelids, and the mucosal lesions are like those in the mouth.

Nail involvement may be manifested as longitudinal striation, grooves, tumefaction of the matrix, or psoriasiform pitting (Gadrat: BsocfrançD 41: 777 1934) The changes are not pathognomonic (Lewis and Ricchiuti: ADS 42 607 1940)





Fig. 1108.—Lichen planus of lips.
Fig. 1109.—Lichen planus of buccal mucosa.

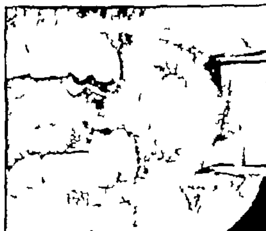
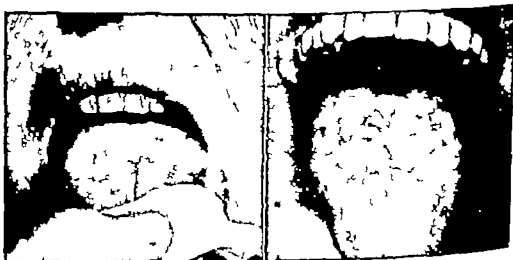


Fig. 1110.—Lichen planus of buccal mucosa. (Thoma: Oral Pathology, Mosby, 19[illegible].)



Figs. 1111 and 1112.—Lichen planus of the tongue. (Thoma: Oral Pathology, Mosby, 19[illegible].)

Volar involvement particularly of the soles may in rare cases become extreme without notable involvement of the glabrous skin. Weber and Rattner (ADS 28 190 1933) saw the palms and soles alone involved, but following roentgen therapy and medication the eruption became generalized and, finally having involuted left slightly pigmented spots. Purplish tint and absence of vesicles are features distinguishing lichen planus from volar tinea.

Lichen planus is generally a persistent disease lasting for 3 months or so and it tends to recur after apparent cure sometimes 10 years later



Fig 1112.—Hypertrophic lichen planus of soles (Dr H. C. Varney)

LICHEN PLANUS IN INFANTS.—Crocker (BJD 12 451 1900) described a type of lichen planus occurring in infants, in which the eruption comes out acutely in groups, the papules being acuminate at first but after removal of the overlying scale smooth, shiny angular and of a brighter red than usual. The sites of predilection are the limbs and trunk (Adamson: BJD 32: 1 1920) Onset was at the age of [illegible] weeks in the baby girl seen by Anderson (BJD 64: 69 195_)

FAMILIAL LICHEN PLANUS probably results from coincidence for there is no reason to suspect transmissibility. See Montgomery and Culver (JCutD 37: 4_, 1919); Saffron (ADS 4[illegible]: 633, 1940); Hellier (BJD 62: 446, 1950); Cassels (ADS 63: 780, 1951)

ABERRANT TYPES OF ERUPTION —Diverse expressions of the disease may escape recognition unless one is familiar with all the clinical aspects lichen planus may assume. The lesions are occasionally circular and consist of closely arranged but more or less typical individual papules. Less common but not less characteristic are cases in which annular lesions develop by gradual peripheral extension from single large papules. One encounters ringed lichen in which papular and annular lesions are present at one time. Sometimes there is an abortive attempt at ring formation by the partial coalescence of several large annular or crescentic plaques of papules for which a suitable designation would be lichen planus annularis hypertrophicus.

See Sutton (J 63: 175, 1914), Chargin and Abramowitz (AD8 1: 329, 1920) Fordyce and MacKee (JCutD 37: 320 1919); Highman and Levin (JCutD 37 130, 1919) Parnet (BJD 34: 356, 1922) Pirila (ActaD-V 5 617 1924) Gougerot nd Civatte (AnndeD 34 5, 1953) histology and rare forms, lichen nitidus a variant of lichen planus

LICHEN PLANUS HYPERTROPHICUS is characterized by the occurrence of rounded or oval, isolated patches which are brownish or purplish in color slightly elevated, rough, scaly dry and intensely itchy The bases are infiltrated and sharply circumscribed. The outer side of the leg is a favorite location. These lesions may persist practically unchanged for years. They result from the coalescence of primary papules, and usually a history of lichen planus of the ordinary type can be elicited. Sometimes a few outlying or satellite papules still remain



Fig 1114.—Hypertrophic lichen planus, on the leg

LICHEN PLANUS HYPERTROPHICUS RETIFORMIS is a rare variety of which Sutton (J 62: 175 1914) has seen 2 instances. One of these had numerous large, purplish papules, with stellate bases, on the *backs of the hands. The lesions* had begun as small, pinhead sized papules many months before and a few of these characteristic lesions were still to be found on the flexural surfaces of the wrists. The bases of many of the larger growths had coalesced at various points, giving rise to a peculiar netlike arrangement which was quite striking Histologically both cases presented the struct ral peculiarities of lichen planus.

LICHEN PLANUS VERRUCOSUS is a comparatively rare type in which the lesions are acuminate or conical, with central horny projections. When coalescent they form a rough, horny greenish or brownish patch.

ERYTHEMATOUS LICHEN PLANUS, originally described by Crocker was observed by Freeman (AD8 13 489 19*6) The lesions in these rare cases are crimson and soft, yet the histologic structure remains diagnostic.

LICHEN PLANUS ATROPHICUS is a rare type in which the papules enlarge peripherally and atrophy centrally unt l eventually the entire lesion thins down and only an atrophic white spot remains. Typ e l involuting l chen planus lesions are present in true cases of this disease wh ch differs from l ch n sclerosus (q v); see Wise and Sulzberger (YBD 1937 p. 236); Miescher (AfDuS 171 419 1935) Montgomery and Hill (AD8 42 755, 1940) While some examples seem to connect lichen sclerosus with morphea guttata, Wise and Rosen (JCutD 35 06, 1917) were convinced that this is not the case. Occasion-

ally secondary hypertrophic and fibrotic changes develop in the subjacent con ective tissue resulti g in lichen planus morphoeens (Stowers) or lichen planus keloidiformis (Pospelow)

Lichen Planus et Acuminatus Atrophicans.—Folliculitis decalvans et lichen spinulosus was identified by Feldman (ADS 34: 378, 1936) as being, in fact follicular lichen planus Some cases of lichen spi ulosus constitute an acuminate and atrophic form of lichen planus (Ellis and Kirby-Smith: ADS 43: 628 1941) This occasions alopecia which lacks the follicular plugs of folliculitis decalvans (Sack and DeOreo: ADS 43 1091 194.) A follicular circumscribed form exists, ffecting parts other than the scalp (Comber and Bluefarb: ADS 44: 46, 1941) See Mezzadra (he BJD 61: 1?5 1949)

Dermatitis Lichenoides Chronica Atrophicans of Csillag is intimately similar to atrophic lichen pl nus, although it was distinguished from this a d from morphea guttata by Wise nd Shelmire (ADS 18: 179 1923) who reported that all the cases they had studied, described as lichen sclerosus, lichen morphoeus, lichen planus atrophicans lichen albus of Zumbusch, white spot disease cardboard scleroderma, scleroderma guttata and lichenoid sclerod rma with atrophy can be grouped under three heads (1) those akin to lichen planus; ( ) those akin to morphea; and (3) those akin t neithe and these last comprise the group of Csillag See Vaughn and Piper (ADS 69: 360 1954)



Fig. 1115.—Lichen planus, with bullous lesions. (Dr A. Benson Cannon.)

Lichen Planus Bullosus.—Minut collections of serum in the prickle layer and in the papillary region are not rare in lichen planus and a n mber of well-defined bullous examples of the disease ha e bee described. Flui l collect t the dermo-epidermal junct re, usually in the vici ity of a coil gland duct. The cause of vesicle formation in these cases is a l t resti g as it is little und rstood. Colcott Fox w the first to suggest that th complication might sometimes be due to arsenic. Engman (JCutD 22 207, 1904) suggested that th development of bullae depends on a unusual tendency t edema, a firm and nonedematous epidermis, and degenerative cha ges in the elastic fibers. Pokorny (DWchn 76 414 1923) believed that the tendency t vesiculation is merely an evidence of extreme intensity of the exudative process. The occasional occurrence f suppuration with without subsequent lceration, may result from staphylococcic infection. I reporti g 3 cases with bullous lesions, 8 others were collected by Strauss (ActaD-V 14: 447 1933) Estrogenic h rmon was helpful i a bullous case f Zugerman and Gross (PaMJ 47 571 1944) Pemphigoid cases, quit rare, were reviewed and one was added t th l terature by Blair (ADS 59 128, 1949)

Lichen Planus Linearis (Lichen Planus Striatus of Crocker) is comparatively rare. Th eruption may consist of a rrow fillet of typical papula lesions resembli g ervus line l teris (q.v) V rious explanations none satisf ctory ha been advanced to account for the peculiar distribution (Senear and Caro: ADS 43: 116 1941) In Mackenzie's case the papules appeared to have predilection for the areas overlying recently thrombosed femoral and saphenous vein ; in Perry s cases the eruption closely followed the distribution of the long saphenous rve i one instance and the external branch of the radial nerve in the othe in one of Crocker s patients there was a band on the left thigh

corresponding with the external cutaneous and anterior femoral nerves The eruption in the patient of Davis (ADS 38: 615 1938) was of zosteriform distributio about the trunk The eruption may follow scratch marks or other local injuries; no such explanation, how ever accounts for the phenomenon. See McGill (JRoyArmyMC 89: 303, 1947)

Etiology—The cause is unknown Nervous exhaustion is thought to be an important contributory factor (Lynch JID 13 43 1949) The disease occurs especially during adult life and it appears to be a systemic one with cutaneous lesions. Without understanding how chronic fatigue acts as a cause I am convinced that it does. Some 30% of the patients are hyper tensive Focal infection may appertain (Chipman J 71 1276 1918) Lichen planus (p 909 see Dermatitis medicamentosa) The studies of Jacob and Sullivan (SouthMJ 36 401 1943) it is comparable with quinacrine lichen

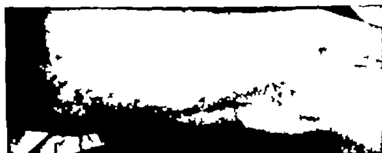


Fig. 1116—Linear lichen planus.



Fig 1117—Linea lichen planus.

planus (p 909 see Dermatitis medicamentosa) The studies of Jacob and Helmbold (ADS 27 472 1933) suggested a bacillus as the cause Postma (ADS 36 826 1937) was unable to confirm their finding

Pathology—Lichen planus papules possess typical structural charac teristics. The horny layer is thickened and condensed, and there is slight acanthosis, with stretching of the prickle cells. The papillae are enlarged, and the intrapapillary vessels dilated. There is a dense sharply defined cellu lar infiltration in the papillary and subpapillary layers. Lymphocytes pre dominate with a number of polymorphonuclear cells, especially in newer lesions. The line of demarcation between dermis and epidermis is rendered indistinct by the dense superficial infiltrate Lipschütz found granular histio cytes which he called centrocytes, among these cells (Olin ActaD-V 15 193 1934) they occur also in pityriasis rosea measles and German measles

In the hypertrophic lesions the hyperkeratosis, acanthosis papillary hypertrophy and vascular changes are exaggerated and the coil glands may secondarily undergo cystic dilation.

Diagnosis—The disease is to be differentiated from psoriasis, lichenified dermatitis, and papular syphilids. Oral lesions of lichen planus do not fluoresce in Wood's light while those of neoplastic leukoplakia do (Costello and Luttenberger NYSJM 46 1778 1946) See Laymon (MinnM 25 863 1942) In psoriasis the papules are scaly from the beginning and the scales are thicker and more abundant Psoriatic lesions enlarge by peripheral extension; patches of lichen planus are formed by coalescence In psoriasis the knees and elbows seldom escape involvement there are minute hemorrhagic points when the scales are forcibly removed and itching is inconspicuous. In contact dermatitis there is vesiculation or lichenification, and the borders are not sharply demarcated. Lichen planus is a dry disease throughout its course.





Fig 1118—Papule of lichen planus, showing superficial lymphocytic infiltration, which fills the dermal papilla and disrupts the dermoepidermal junction

Fig. 1119—Bullous lichen planus, showing subepithelial separation of epidermis and dermis. Note cohesion of sweat duct despite vesiculation.

The miliary papular syphilid sometimes resembles papular lichen planus, but the color distribution absence of itching concomitant lymph node involvement and presence of a positive serum reaction render diagnosis clear

Prognosis.—Lichen planus is an exceedingly chronic disease but one which usually clears eventually

Treatment.—The patient should have the benefit of good food, hygienic living and, if it can be attained, freedom from worry or care. Reduction of caffeine ingestion is conducive to better rest

Mercury is an efficient medicine best given into the gluteal muscles:

℞	Mercuric salicylate	5.0
	Lanolin	4.0
	Olive oil	to 30.0

Sig. Mercury salicylate in oil 1.0 cc. equals 1 grain dose. Shake and inject aseptically 1 cc into the gluteal muscles every 3 days, if tolerated.

Response to treatment with mercury so impressed Lusk (JCutD 19: 223 1901) that he thought lichen planus perhaps a syphilid.

Bismuth is almost as effective as mercury and may be given by mouth as Bistrimate (Wright and Gross ADS 61 489 1950) Acetarsone is often effective in tablets of 0.25 Gm., the maximum dose being 2 at a time 3 times a day for 4 days of each wek for 6 weeks (Sézary and Horowitz BSocfrançD 1936 p 1761 Hufschmitt ib 44 360 1937) It often provokes intestinal cramps and its use entails all the dangers of the arsenicals. The agent so used is of notable utility in some cases, worthless in others, well worth trial in the stubborn ones. Bismuth arsphenamine sulfonate, 0 1 Gm intramuscularly was advocated by Conrad et al (SouthMJ 33 721 1940) Vitamin B complex by injection is a useful adjuvant (Burgess CanadMAJ 44 120 1941) Vitamin C 100 mg daily may be prescribed. Locally x ray therapy in fractional doses abets systemic efforts. Given over the spine x ray therapy was recommended by Driver (ADS 20 201 1921) but Hellier (BJD 55 11 1943) considered this no more effective than mercurial injections. Sonck (Finska Läk SällskH 79 702, 1936) believed that x ray and bismuth were about equally effective curing some 40% helping an equal proportion and failing to benefit the remaining 20% while arsphenamine benefited 30 per cent and failed in a like number

Pernet (WLondonMJ 28: 88, 1923) as well as Pautrle (BSocfrançD 34: 671, 1927) reported good results following spinal puncture. See Schöfeld (DWehn 93: 1197 1931)

Thiamine 100 mg t.i.d., sometimes seems beneficial.

Pyribenzamine or Benadryl may afford good palliation of itching Peck (1947) told me, and he sometimes gave aminophylline or nicotinic acid to obtain vasodilation which he thought helpful A vitamin K like substance was recommended by Pirila (ActaDV 31: 5., 1950)

Cortisone sometimes helps, but it effects in lichen planus are erratic.

Roussel (SouthMJ 29 811, 1936) thought *pituitary extract helpful* in raising the blood pressure and so combating weariness and malaise Stillians (ADS 13 819 1926) has found some form of therapeutic light the most consistently successful method of treatment. On the scalp he employed .5% and stronger alcoholic solutions of Euresol to be repeated after exfoliation was complete. C. J White spoke highly of ultraviolet radiation, front and back and laterally with the arms raised, so as to expose the entire body daily

Chloroquin seemed effective in a few cases and worthy of further trial, reported Ayres and Ayres (J 157 136 1955) who attempted no explanation of it empirical utility

Hormonal influences were discussed by Lancaster (SouthMJ 4 : 1198, 1954) who had a bullous case that responded to estrogens.

Mucosal lesions are notoriously stubborn. It is fortunate that they apparently are inconsequential Fox (ADS 24 1071 1931) found lichen planus of the mouth resistant to all kinds of treatment but Morgan (1952) exhibited a man whose oral lichen planus resolved when estrogenic hormone was given.

I think Premarin has helped a number of my patients, male and female

It is essential that foci of infection be eradicated. Routinely one should examine the teeth by x ray and order removed all dead and abscessed ones, and request treatment of pyorrhea when it exists, and investigate the pelvis and cervix uteri or prostate

For topical treatment, nothing put on does much good, but an ointment may be prescribed as follows

℞	Phenol	0.3
	Ammoniated mercury ointment 5%	1.0
	Zinc oxide	
	Starch	of each 4.0
	Petrolatum	to 30.0
Sig	% ammoniated mercury paste. Apply several times daily	

A soothing nongreasy application which the patient may apply at will is phenolated calamine lotion to which may be added from 1 to 3% alcoholic solution of coal tar Castellani s paint has some utility for coalescent patches.

X ray therapy affords the surest way of obtaining relief The dose one chooses is 100 or 125 r and this may be given weekly over several areas at

each treatment, avoiding detrimental effects on the blood and giving proper attention to the cumulative dose which should seldom exceed 800 to 1 000 r on any given area.

In lichen planus hypertrophicus, numerous methods for the eradication of thick, scaly patches have been suggested none of which is entirely satisfactory Repeated freezing with solid carbon dioxide often is beneficial, and Fordyce and MacKee (1919) spoke highly of roentgen therapy They found that in the majority of instances it would arrest the itching and cause involution of the lesions in a few weeks. The long-continued application, under rubber or oiled silk, of ointments containing considerable percentages of salicylic acid and tar occasionally results in cure Physical methods, including sand paper and fulguration, may be used. In one case the lesion of the thigh apparently was etiologically associated with varicose veins, the occlusion of which seemed to cure the patient (Den e and Coombes ADS 61: 131, 1930)

See Grossman (ADS 28: 46, 1933), bismuth Tanock et al (BrocfrancD 46: 862, 1939), nicotinic acid Koltai (DWchr 109: 1268, 1939), grenz ray therapy of oral lesions; Baird (NEngJM 226 986, 1942) review; Forman (BJD 57 153, 1945) case made worse by gold therapy; Lieberstein and Wechtel (ADS 53: 385, 1946) autogenous antigen immunization; Winer and Levitt (ADS 56 437 1947) in Negro, histology Bechet (ADS 57 496, 1948) lichen planus ocreaformis f Liebenthal, Pierini and Borda (be BJD 63: 372, 1950), pseudopelade end stage of lichen planus; Dostrovsky and Sagher (ADS 59 308, 1949) Palestine cases Herrman (ADS 63: 649 1951) Vitamin A therapy; Hyman and Erger (ADS 64 668, 1951), lichen corneus hypertrophicus, lichen ocreaformis, lichen myloidosis and lichen ruber moniliformis, nosology Hard d Holmberg (be YBD 1954 p 73) response in 75% of 79 cases following large doses of penicillin.

Quinacrine (Atabrine) Lichen Planus (Atypical Lichen Planus of the Southwest Pacific)—During World War II many cases were seen of a peculiar dermatosis. The patients were military personnel who had been on

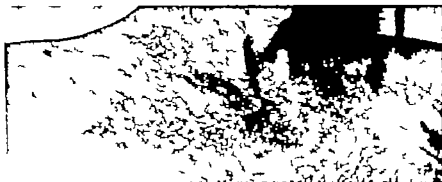


Fig. 118.—Lichen planus-like eruption attributed to quinacrine, Southwest Pacific patient

quinacrine for suppression of malaria for 3 months or more usually on K or C rations in a tropical climate and who had lost from 10 to 50 pounds in body weight (Bereston JID 7 69 1946) New Guinea cases usually started on the dorsa of the feet as an indurated erythema suggesting contact dermatitis or pellagra After a time an abrupt change would occur with exudation and dissemination resembling infectious eczematoid dermatitis, widespread and including the scalp where spotty alopecia was typical and with lymphadenitis as in exfoliative dermatitis. Lesions similar to hypertrophic lichen planus evolved affecting by preference the flexor aspect of the forearms inner thigh regions, buttocks, and dorsa of hands and feet. These phases well described by Goldberg (J 130 775 1946) were not always separated chronologically Dry cases quite like severe lichen planus occurred. Volar involvement was often marked (Barker ADS 55 256 1947) Depigmentation and sometimes atrophic scarring were seen. Italian cases were recognized by Peterkin and Hair (BJD 58 263 1946) Rectal lesions were seen by Warin et al. (BJD 60 249 1948) Atrophy as in atrophic lichen planus was sometimes induced, and this was permanent in at least some of the cases of Shamberg (JID 17 85 1951 21 279 1953) Post Atabrine dermatitis can cause prolonged disability All the cases I saw appeared to recover completely

Figs. 1121 and 1122.—Quinacrin dermatitis, resembling lichen planus.



Fig. 1123.—Hyperkeratotic discrete and confluent lesions of "Southwest Pacific lichen planus." (Photographed August, 1944 by Dr. Morton R. Kahn.)

The exact etiologic mechanism was never clarified, although quinacrine played seemingly an essential role A husband and wife who changed their antimalarial from quinine to quinacrine developed this condition, reported Mitchell (ADS 51 353, 1945) whose identifi tio of the relationship between the drug and the rash was probably the earliest on record although Morton Kahn, stationed t Lae, New Guinea, reported such cases to his superior officer in April, 1944, he told m I believe (ADS 56 26 1947) along with Wilson (ADS 54: 57 1946) that nutritional deficie cy induced both by Atabrine and by the circumstances of the perso el who received it was tiologically of great importance (see chronic lichenoid dermatitis) Positive pat h tests were reported by Duemling (ADS 53: 50 1946) Fla es following readministration of quinacrine were inconstant, Bagby (ADS 5- 1, 1945) observing none d Bazemore t al. (ADS 54 308, 1946) reporting provocation in about 20% Since pure dermatitis medicam tosa m y be expected to flare in 100% of cases on readministration of the causative drug the way in which quinacrine caused this disease must have been oth than by ordinary idiosyncrasy (Schmitt et al.: ADS 53 226 1946) Blood quinacrine co centration diminished parallel with itching after cessation of th drug (Bigham: BJD 58: 271, 1946)

In treatment, removal to temperate climate penicillin, yeast, vitamin B complex, and elimination of quinacrine were effective measures and pig mentary abnormality proved temporary I should expect high protein diet, cortisone and vitamin B_{12} to prove effectual if such cases again show up and they may be expected from quinacrine therapy of lupus erythematosus.





Fig. 1124 —Patchy alopecia in "Southwest Pacific lichen planus (Dr Morton R. Kahn)
Fig 1125 —Lichenoid dermatitis of the ankles in "Southwest Pacific lichen planus. (Dr Morton R. Kahn.)

See dermatitis medicamentosa, quinacrin ; Epstein (BullUSAMD 4: 457 1945), quinacrine syndrome, relation of tinea and dermatitis venenata Surgeon General' Office (BullUSAMD 5 453, 1946) untoward reactions to quinacrine; Livingood et al (J 129 1091, 1945) Nesbit (ADS 53 221, 1946) penicillin for secondary infection, hypertrophic, exudati e and ex foliative types Mitchell (ADS 53 199 1946) case, nodules on hands, (YBD 1946, p. 210 ff) abstracts of rticles on this condition; Fereston and Cheney (ADS 54 425, 1946), treat ment; Decker (ADS 54 318, 1946) eczematoid reaction to Atabrine, no fluorescence in lesions; Pillsbury and Livingood (ADS 55 441 1947) description; Loewenthal (ADS 56 868, 1947) priority of recognition of syndrome; Poindexter (JN tionalMA 39 146, 1947) "jungle rot"; Alden nd Frank (ADS 56 12, 1947) 60 cases Nesbit (J 134 446, 1947) review Benedek (UCutRev 51 207 1947) avitaminosis A due t Atabrine Williams (BMJ 2 801 1947) in Australian and New Zealand troops Butler (ADS 56 535, 1947), sev re systemic symptoms in some cases Nelson (ADS 55 12, 1947) 12 cases Mitchell (ADS 57: 434, 1948), the patient presented by Rencar and Caro (ADS 51 353, 1946) Costello (ADS 57: 551 1948), atrophic case; Singh (BJD 60 90, 1948) 83 cases in Indian laborers; Tait (BMJ 1 375, 1949); Schmitt (ADS 59 16, 1949) 6 cases; Bigham (BMJ 2 387 1949) similar syndrome caused by gold; Miller et al. (JID 15 445, 1950) when Atabrine is given, sweat ducts and hai follicles become fluorescent; Perkins (AustralJD 1 75, 1951)

LICHEN NITIDUS

Lichen itidus i rare, hro ic, inflammatory derm tosis, manifested by papular lesions, characteristically firm, flat topped, shiny pinhead-sized, and pinkish o flesh colored, which seldom coalesce or give rise t symptoms. The favorite site f involvement th genit l region nd the bdomen, breast d arms re sometimes attacked. Indi vid al papules bea striking resemblan e to those of liche planus, but thei color distri bution and bsence of tching are distinctive.

There are 2 varieties of the disease, wrote Niles (ADS 22: 687 1930): (1) one showing a histologic resemblance to tubercle formation and having an apparent relationship to tuberculosis elsewhere in the body; and (2) one which clinically exhibits no etiologic relationship with tuberculosis and which shows the histologic picture of nontuberculous, inflammatory granuloma. The association of lichen nitidus with lichen planus is being more frequently reported, according to Ellis and Hill (ADS 38: 569 1938) who, adding 2 such combined cases, recited the similarities of the two diseases.

The lesions are persistent and may remain for years without change. The rash was severe confluent on the trunk and cleared only briefly during an intercurrent appendicitis, in a 9-year period in the case of Ayres (ADS 4 ?96 1943). The eruption was of the rare, generalized type in the case of Alexander (DWchs 8?: 09 19?6). In cases seen by Barber (BJD 37: 276 529 1925 38: 143 ?93, 19?6) the lesions became confluent. In the case of Wien and Perlstein (ADS 30 700 1934) the eruption began on the knees and elbows and gradually spread over all the extremities. The patient of Trimble (ADS 1 468 1920) was a Negro and a Negro girl with lesions only on her face was reported by Barsky and Schorr (ADS 6?: 572 1950). The Koebner phenomenon was observed in cases by Plakas and Shair (ADS 66 8. 195.)

The cause is not known. Treatment is usually neglected or symptomatic only. Tuberculin injections appeared curative in a patient of Gougerot and Burnier (BsocfrancD 41: 650 1934). Gold given intravenously cured Niles patient.

Fig 1128—Lichen nitidus (Dr Stuart C. W y)

LICHEN SPINULOSUS

Lichen Spinulosus (Lichen Pilaris Seu Spinulosus) is a disorder which resembles keratosis pilaris. As first described by Crocker in 1883 (according to Adamson BJD 17: 39 77 1906), the condition is an inflammatory disease of the hair follicles, in which a spiny epidermic peg occupies the center of the papule (cf Crocker (Diseases of the Skin, Blakiston 1908 p 45.). The majority of the patients are children, and the lesions, which are pinhead-sized, conical, spinous papules, generally develop acutely or in crops and may persist indefinitely. There is some hyperemia at first, but this gradually subsides, and the lesions become grayish or yellowish in color. Subjective symptoms are slight or altogether wanting. The sites of predilection are the back of the neck, the trochanteric region, the abdomen, the thighs and the extensor surfaces of the arms. The cause of the disorder is not known. Histologically Crocker found congestion of the vessels, followed by slight effusion around the follicle, and hypoplasia of the epidermic cells surrounding it.

The problem was reviewed by Feldman (ADS 34: 374 1936) who felt that most if not all, cases reported under the name folliculitis decalvans et lichen spinulosus indeed are forms of lichen planus, and that disorders diagnosed lichen spinulosus are often keratosis pilaris as lichen planus. MacLeod (BJD ?0 85 1908) described filiform spines in association with lichen planus, lichen scrofulosus, the miliary papular syphilid and seborrheic dermatitis. Follicular hyperkeratosis characterizes lack of vitamin A. This nutrient substance appeared to be curative in the cases of G rfield (ADS 45: 423, 1942)

LICHEN STRIATUS

Lesions of linear configuration are seen in various dermatoses the majority of cases bei g examples of nevus unius lateris, occasionally of lichen planus; but certain cases of a simple dermatitis, usually lichenoid, deserve separation as a distinct clini al group, according to Senear and Caro (ADS 43: 116, 1941) whose re iew of the literature and 10 cases personally observed form the basi of my description. Pinkus (DZtschr 11: 19, 1904) recognized 2 cases affecting the thigh and the forearm. Th onset is sudden, ex tension of the eruption to f rm linear bands is r pid, and the efflorescence fades with bland treatment or no treatment at all within a few months. The upper extremity is the usual location. The patient is usually a child. The elements of the lesions are lichenoid papules primarily small and discrete but not like those of lichen planus. Coalescence results in patches of erythematosquamous d rmatitis. The bands may be continuous or segmented and irregular in width. They are relatively asymptomatic, although some burning and itching ma be present at the onset as in the case of Netherton (ADS 50: 341 1944) When they in olute they leave no trace. Histologic changes are nonspecific.



Figs. 1137 and 1138.—Lichen ruber moniliformis. (Wise nd Rein ADS 34: 830 1936.)

The cause is unknown. Lichen planu was coincidentally present in the case of Pinkus (JID 11: 9 1948) but there was o indication that the o e disease underwent tra sforma ti n into the other. No treatment is necessary for none is known to be effective, and th course resol es in pontaneous healing in a few months. See Johnson (ADS 53: 51, 1946); Bothma and Niederman (ADS 54: 748, 1946); Semon (BJD 62: 500 1950) quee zonal d rmatoses Lan (Lancet 1: 616, 1951)

LICHEN RUBER MONILIFORMIS

The papular lesions of this extremely rare d rmatosis are arranged in narrow beaded band ru ing more less parallel with each other i the long axis of the extremities. Wise and Rein (ADS 34: 830, 1936) reviewed the subject exhaustively nd were con vi ced that only Kaposi original case and their own, of 17 in the literat re were alike. Th dissimilarities with lichen plan s, which they thought wa not related to morbus mon liformi lichenoides, the title they preferred, included the keloidlike lesions and th bsence of the histologic structure of lichen planu Afte topsy of this pa tient they (ADS 38: 31, 1938) were still unable to explai the nature of the disease. Harper (ADS 20 01 1929) described a similar disorder i a wom n of 77 years: the lesions w re dome-shaped papillae, yellowish and pinkish in color rranged in beadlik rows, nd hist logically there wa degeneration of the collagen with associated fibroelastic prol f ration. Nékám (PresseM 46: 1000, 1933) reported a remarkabl example of the disease. Th hanges were myxedematoid in the chronic and widespread eruption of a wom n studied by Ba ber (BJD 55: 209 1943) The lesions of the lower extremities in a young woman reported by Pinkus and Pinkus (ADS 54: 472, 1946) simulated those of

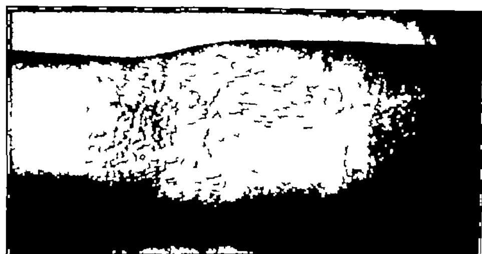


Fig 1129.—Lichen ruber moniliformis. (Wise and Rein ADS 34 830 1936.)

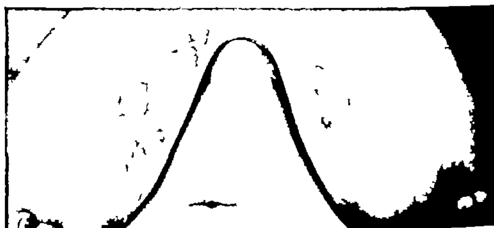


Fig 1130.—Lichen sclerosus et atrophicus. (Dr J Lamar Calloway)



Fig 1131.—Lichen sclerosus et atrophicus of penis. (Drs. Montgomery and Hill)

Fig 1132.—Balanitis xerotica obliterans

Fig. 1133.—Lichen sclerosus et atrophicus showing hyperkeratosis, keratotic plugging related to sweat ducts, liquefaction necrosis of basal layer, [illegible] lymph [illegible] edema, homogenization of upper dermis [illegible] infiltration of [illegible]. (Drs Montgomery and Hill)

erythema ab igne; this patient subsequently showed considerable improvement when Thorazine was given in a dose of 75 mg daily (Pinkus: AD 71: 543, 1955)

See McFarland (ADS 55 674 1947) 2 cases, Miller (ADS 52 129 1945) lichen verrucosus et reticularis of Kaposi (VrtljschrfD 13 571 1886)

LICHEN SCLEROSUS ET ATROPHICUS

The disease was first described by Hallopeau (AnndeD 8 790 1887 10 447 1889 7 57 1896 9 358 1898) who thought it to be a variant of lichen planus (Gahan ADS 69: 435 1954) It was segregated from morphea guttata as a distinct type of lichen planus by Montgomery and Ormsby (JCutD 25 1, 1907) and identified as lichen planus sclerosus et atrophicus (Hallopeau) by Ormsby (J 55 901 1910) in a review of the literature to which he added 8 cases. Hallopeau's disease was considered to belong to the lichen planus group by Wise and Shelmire (ADS 18 179 1928) Complete separation of lichen sclerosus from lichen planus was subsequently made

The characteristic lesion is an irregular often polygonal flat-topped, white papule of a color comparable with ivory or mother-of-pearl. The papules are firm neither elevated nor depressed, or only slightly elevated. Generally no areola is present, but a rosy or moderated pigmented areola may surround the papules. These may be discrete or grouped, and most cases present both types. When grouped to form plaques, the outline of the individual papules forming the plaques can be determined. Each papule has on its shining smooth surface from one to several dark horny comedo-like plugs, or minute bead like depressions which show the sites of former plugs. These are situated at the pilosebaceous or sweat pore orifices and are important from the view point of diagnosis, wrote Ormsby quoted by Montgomery and Hill (ADS 42 755 1940) The disease is of insidious onset with minimal subjective symptoms, affecting middle-aged and older persons as a rule women several times as frequently as men. It evinces preference for symmetry of location and involvement of the genital and perianal umbilical, anterior thoracic scapular and anterior wrist regions. Similarity to morphea and to atrophic lichen planus is considerable Depigmentation and sharp delineation are features, and while induration is palpable in the early stages, when the lesions may be somewhat edematous atrophy generally eventually ensues, with fine wrinkling of the surface The formation of bullae is not unusual, liability to this phenomenon being comprehensible from the microscopic alterations, for separation of the epidermis occurs in much the same manner as in epidermolysis bullosa Then the lesions become painful and subject to secondary infection.

An e treme bullous exampl w s reported by Gottschalk and Coope (ADS 55 433, 1947) and ther by Anderson (ADS 49 423, 1944) Carcinoma does not arise from th vul ar lesi ns of lichen sclerosus, insisted Wallace and Nomland (ADS 57: 240 1943) nd the latter disease when it affects the vulva, is never confined to that location.

Lichen Sclerosus in Children is not extremely rare The 3 patients of Laymon (ADS 52 331, 1945) were g ls younger than 6 years of age. Kindle (BJD 65: 269 1053) reported 8 cases in which th disease appeared between the ages of d 13 years. In o l 1 of these were lesions present elsewhere than on the nogenital tissues. A occasional hemorrhagic bull ppeared on the l in se eral patients. In cases the disease spontaneously i vol ted within years.

Balanitis Xerotica Obliterans wa shown to be lichen sclerosus affecting the glans peni by La mon nd Freeman (ADS 40: 57 1944) who sought and fou d other lesion in 4 of 6 patient whose penile involvement w their complaint. When the glan l affected, sclerosi nd contract re f the meatus result l t rf ring with micturitio and requiri g dilation or surgical largement of the rifice Grutz (DWehn 105: 1206 1937) described thi condition Stühmer bala itis, which l characterized by mild chronic inflammation w th atrophy d adhesion, and ttributed it to irritating disinfectants, but Schubert (DWeh 105: 1633 1937) recog ized it a disease *sui generis* diff ring from sclerosi ma nd lichen pla s. Identity with kra rosis was post lated by Freem n a d Laymon (ADS 44: 54 1941) whose histolog e st l es d ff re tiated it from leukoplakia. Discussing thei pape C le ecommended a trial of estrogenic hormo e s ther apy Testost ron ol tne t w beneficial in a c se reported by Wigley (BJD 58: 240 1946) d cases of Showman (SouthMJ 42: 385, 1949) were partially responsi e to lrogen.

Figs. 1124 and 1125.—Lichen sclerosus et atrophicus: umbilical lesions of a man 37 years old and anovulvar lesions of a woman of 65. (Montgomery and Hill: ADS 42: 755, 1940.)





Fig. 1126.—Lichen sclerosus et atrophicus, affecting vulva and perineum of a girl 10 years old. (Kindler: BJD 65: 269, 1953.)

Fig. 1127.—Lichen sclerosus with meatal stricture. (Dr J Lamar Callaway.)

Histologically the typical change is lymphedema in the upper cutis with nonmucinous homogenization and edematous alteration of the connective tissue fibers beneath the epidermis. Elastic tissue fibers are not destroyed but are separated from the epidermis. There is a lymphocytic, plasma and mast cell infiltrate in the midcutis beneath the area of edema. Deeper blood vessels are not obliterated, a distinction from morphea. Epidermal changes are apparently secondary and comprise hyperkeratosis, keratotic plugging of the follicles and dermal appendages, atrophy and flattening and loss of the rete ridges. Mild liquefaction degeneration of the basal layer accompanies the superficial dermal lymphedema.

Treatment.—Since the cause is unknown, although sex hormone metabolism is evidently concerned, therapeutic effort has been symptomatic. Most cases are asymptomatic and ordinarily the patient needs to be offered little.





Fig. 1129.—Lichen sclerosus, showing atrophy of superficial dermis. (Dr. Isaac Pels.)

Fig. 1130.—Atrophic lichen planus, showing inflammatory changes in superficial dermis, in contrast with lichen sclerosus. (Montgomery and Hill: ADS 42: 755, 1940.)

Friction and trauma should be avoided lest they provoke bulla formation. When bullae have formed, talc and protection generally suffice to enable healing to occur. Vulvar cases resemble kraurosis and are sometimes symptomatically distressing, but treatment other than vulvectomy has been palliative and on the whole unsatisfactory. Estrogen applied topically persistently as Premarin cream is curative. Anderson (pers. comm., 1948) told me: While the dermatosis is ordinarily practically asymptomatic, its presence discloses estrogen deficiency, and the patient usually feels much better when a balanced dose is given orally, and the skin may be expected to improve.

See Borda and Delton (The YBD 1942, p. 317). Leifer (ADS 49: 118, 1944): balanitis case; Mota (The YBD 1944, p. 221), Stühmer's balanitis; Ingram (ADS 50: 120, 1944); Negrete Lara (Dermatologica 93: 159, 1946): Miescher's classification of "white spot disease"; Fox (ADS 57: 514, 1948): urinary meatus involved, only; Miescher (Dermatologica 97: 93, 1948): classification; Welton and Newlin (ADS 59: 636, 1949): balanitis provoking dyspareunia; Laymon (ADS 64: 620, 1951): review, distinction from lichen planus; Stahle and Pound (AustralJD 1: 160, 1952): 4 cases, histology.



Fig. 1140.—Seborrheic dermatitis of scalp and ear.



Fig. 1141.—Seborrheic dermatitis, neck.



Fig. 1142.—Seborrheic dermatitis, calf.



Fig. 1143.—Seborrheic dermatitis, palm.

SEBORRHEIC DERMATITIS

Symptoms.—The common form dandruff affects the scalp and is characterized by diffuse scaliness, the scales being greasy and yellowish

The lesions may be dry with grayish, branny scales or they may be oozing and crusted constituting the eczema capitis of older writers. Superinfection accounts for the weeping however it is thought and streptococci staphylococci and contactants commonly complicate seborrheic dermatitis. From the scalp the disease often spreads to the forehead, brows, nose and cheeks, so constituting the dry skin of cosmeticians. Psoriasiform patches may occur in the axillae over the sternum, about the umbilicus and in the crural folds The margins of the eyelids are involved in many cases (Clark AmJOphth 20 808 1937) and blepharitis may be severe even though disease in the scalp is comparatively inconspicuous.

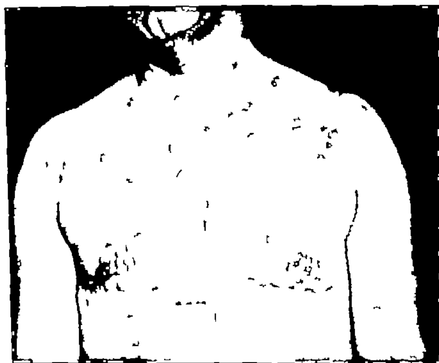


Fig. 1144—Seborrheic dermatitis of psoriasiform type, with typical involvement of sternal area. (Dr F Ronchese)

Alopecia does not result from dandruff I am convinced but in alopecia accompanied by dandruff treatment for seborrheic dermatitis may be justified.

Streptococci may produce scaling intertrigo and postauricular fissuring distinguished only with difficulty from seborrheic dermatitis.

Acne vulgaris is usually complicated by pityriasis capitis and pityriasis of the face This might be due to the fact that *Pityrosporum ovale* is a lipophil fungus and finds the oily skin of the acne patient a ground where it luxuriates (Benham JID 2 187 1939 Emmons: PHRpts 55 1306 1940)

Pruritus ani et vulvae is sometimes due to seborrheic dermatitis which in the scalp deserves treatment in problematic cases of anogenital dermatitis.

Scurf scalp in infant is sometimes due to seborrheic dermatitis contracted presumably from the mother It may also represent an accumulation of corneous and oily detritus resulting from the application of baby oils and the disinclination to rub the scalp with sufficient vigor to cleanse it (Gordon: BMJ 1: 333, 1940)

Seborrheid is the name applied to disseminated rashes in persons with seborrheic dermatitis of the scalp seco dary thereto. These are seen especially in the wintertime and when the scalp infection is heavy The lesions are small, generally dry discoid, and located by predilection on extensor aspects of the extremities resembling the lesions of dermatophytid or of winter itch (Niles ADS 39 474, 1939) They are rough to the touch but otherwise practically asymptomatic. The eruption generally responds promptly to treatment of the scalp and locally a mild coal tar ointment.

Etiology—Excessively oily foods, particularly milk cream butter chocolate and cod liver oil are a predisposing factor and hypothyroidism is also. *Pityrosporum ovale* may be as profuse in scalps of normal appearance as in those showing severe dandruff according to MacKee et al. (JID 1 131 1938 2 37 1939)

Sabouraud (quoted by MacKee et al.) reported the following bacteriologic findings: (1) in pityriasis (simplex) sicca, *P ovale* i plentiful; ( ) in pityriasis (simplex) oleosa, *P ovale* is present, and may or may not be accompanied by *Staphylococcus albus* (3) in seborrhea oleosa, *P ovale* and taphylococci are present, the microbacillus, too, if the hair is falling but without it if the hair is healthy (4) in pityriasis circinata (seborrheic dermatitis) *P ovale* is usually present, and hair loss is not a feature.

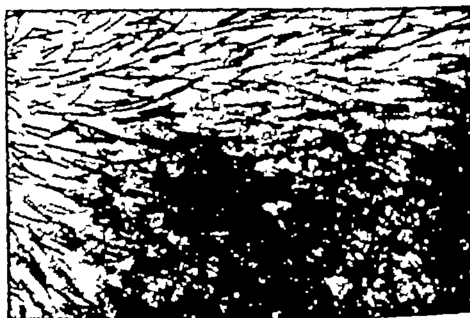


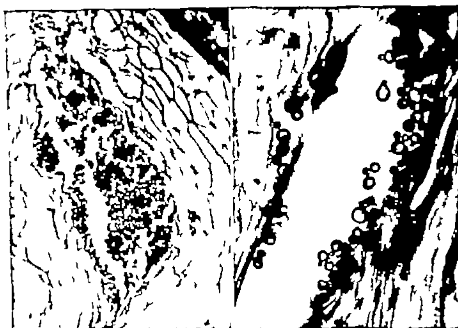
Fig 1148—Seborrhei dermatitis of scalp "dandruff. (Dr Morris Moore)

Pit rosporum can be seen in teased potassium hydroxide preparations or stained scales. Most of the cells are ovoid or spherical with or without buddi g, being from 2 to 4 μ a lo g ax s, sometimes larger Moore (ADS 31: 661, 1935) cultivated the organism from sc les on Difco wort agar the first growth being small grayish white colo ies which when transpla ted to a th cke part of the medium developed into cultures of ocherous salmon to pinkish buff col r

The organism might be the cause of the disease suspected Kile and Engman (ADS 37 616, 1938) but at present there is great doubt regarding the veracity of this view (Whitlock BMJ 1 484 1953) Discussion of the etiologic relation of *P ovale* t seborrheic dermat tis is good a given by Lewis and Hopper (Introduction to Medical Mycology 1948, p 34.) No pathogenicity was discernible when i oculation experiments were performed by Rocha et al. (JID 19 239 1953) nor did intradermal tests with two different antigens reveal sensitivity

The disease must be parasitic for it behaves clinically as if it were transmissible. This view was upheld by Blake (abs Lancet 2 1376 1890) who was aware of the significance of dandruff in blocking sebaceous orifices and thereby contributing to the cause of acne.

Whether *P. ovale* is or is not the actual cause the practitioner can successfully manage seborrheic dermatitis if he treats the scalp as if it were suffering from a form of parasitism to which immunity does not develop and which is almost universally distributed among human beings and which affects some people more than others because of individual variations in oiliness of the scalp and in nutritional and endocrine adequacy



Figs. 1146 and 1147.—*Pityrosporum ovale* in sections of scalp, high magnification. (Dr Morris Moore.)



Fig. 1148.—Seborrheic dermatitis, showing scaling and superficial dermatitis.

Chemical studies of the skin fat in seborrheic dermatitis were made by Hodgson-Jones et al (BJD 65 246 1953) who found differences from normal suggesting a derangement of the metabolism of sebum the iodine number and squalene content are lowered, the cholesterol content is raised, and the cholesterol-squalene ratio is markedly altered

Treatment.—It may be advisable to put the patient on a low fat diet (Amshel PaMJ 45 457 1942) omitting particularly milk and ice cream. Some patients need thyroid and are helped by it Vitamin preparations, especially those rich in the B complex with emphasis on riboflavin and B_{12}

(Andrews et al NYSJM 50 1921 1950) and injections of liver extract (Sayer UCutRev 46 719 1942) are also often helpful. I have seen improvement follow the use of ascorbic acid 100 mg with meals. When the scalp is excessively seborrheic Premarin in suitable dosage may help

Topically on the scalp a valuable prescription is

℞	Phenol	1.0
	Mercuric chloride	0 1
	Resorcinol (or resorcinol monoacetate)	8 0
	Alcohol (70%)	to 180 0

Sig: Rub into scalp several night a week as directed, particularly after each shampooing Shampoo every 7 to 14 days. Use no brush because it cannot be sterilized satisfactorily Use a cheap new comb after each shampoo to avoid reinfection.

An ointment to be rubbed into the scalp is messier than the liquid but is sometimes more effective

℞	Salicylic acid	1.0
	Ammoniated mercury (or precipitated sulfur)	[illegible]0
	Rose water ointment (or Carbowax 1,500)	30.0

Sig: Rub in thoroughly one evening a week shampoo the next morning with ordinary soap.

There is no virtue in medicated soaps or special shampoos. On the body in widespread cases complicating dermatitis venenata an ointment rarely irritating particularly useful in hospitalized patients is

℞	Crude coal tar	0 3
	Lanolin sufficient to mix	
	Petrolatum	to 30 0

Sig: 1% crude coal tar Rub in twice a day for 3 days.

This peels off the seborrheic dermatitis much as chrysarobin peels off the lesions of psoriasis, but it does it more gently A selenium disulfide preparation, Selsun, was introduced in 1951 and has it would seem considerable usefulness (Slinger and Hubbard ADS 64 41 1951) Selenium sulfide ointment 1% was effective but sometimes irritating when applied to lesions of the glabrous skin by Ayres and Ayres (ADS 69 615 1954) An ointment containing pyridoxine may work in the dry type of the disease (Schreiner et al JID 19 95 1952) The drug is useful only topically Hydrocortisone ointment to which 2% sulfur may be added, may prove effective especially in treating the skin of the auditory canal when it is involved

Dermatitis venenata particularly if it involves the neck or face and is of long duration, is readily complicated by seborrheic dermatitis. The combination resembles so-called lichenified eczema It may be cured by first allowing the moiety of the dermatitis which is due to chemical irritation to heal by using bland soothing applications and avoiding all irritating contacts, then one may use crude coal tar or some other suitable antiparasitic remedy for the remaining parasitic irritation. By interpreting many of the otherwise obscure cases of eczema in this manner I am able to cure patients nowadays who were at one time seemingly insurmountable therapeutic problems.

See Templeton (ADS 14 2 0 1926) culti tion of P ale Acton and Panj (IndMJas 62 602, 1927) linical feature , M cLeod and Dow ing (JID 40 139 1928) microsporon of Malassez, Moore and Kile (Hel 81 277 1935), pathogenicity of P ale Moore [illegible] (ADS 33 457 1936) cultivation of P ov le, Parel al (BMJ 2 834 1936) seborrh[illegible] entiated from pityriasis capitis, Sabouraud (Nouv lle Prat[illegible] Dermatologique 7 [illegible], 1936 Masson) Perey l (BJD 51 7, 1939) seborrheic dermatitis Dowling (BJD 51 1 1939) cause undetermined, secondary infection frequent Wise and Sulzberger (YBD 1941, p 7) review and therapy Price (CanadMAJ 56 26, 1947) clinical features d therapy; Martin-Scott (BJD 64 257 1952), culti tion of P ovale Spoor et L (ADS 69 323, 1954), cultivation of P ovale the habitat f which is not limited t scalp, to diseased kin, or to human beings Pachtman et al (JID 22 389, 1954), no rel tion of seborrheic dermatitis t number of kinds of bacteria Hereston (J 156 1246, 1954) selenium sulfide shampoo fficient [illegible] 140 cases followed for 2 years

PSORIASIS

Symptoms.—Psoriasis is a chronic relapsing disease of unknown cause, characterized by the eruption and persistence of reddish rounded lesions, usually dry and covered with silvery imbricated scales. The disease affects persons of either sex and any age. It commonly appears in early adult life first in the scalp then as a symmetric eruption which involves by predilection the extensor surfaces of the limbs, particularly elbows and knees. The primary lesion is a flat topped papule which quickly becomes covered with a



Figs 1149 and 1150.—Psoriasis. (Dr J P Guequierre.)





Fig 1151.—Psoriasis. (Dr A B Cannon.)
Fig. 1152.—Psoriasis, guttate. (Drs. Kessler and Kessler.)

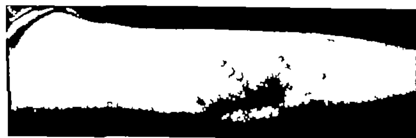
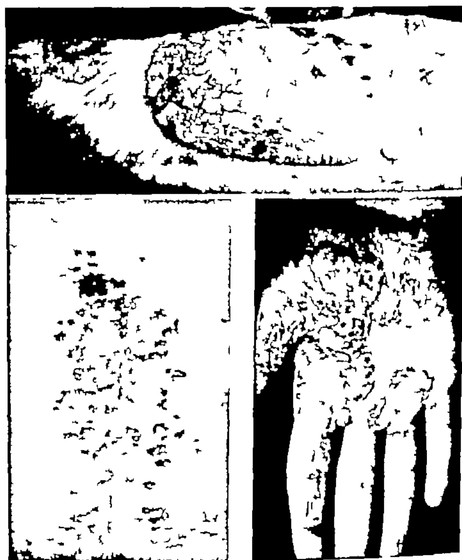


Fig. 1153.—Guttate psoriasis of elbow region.

thin, whitish scale. Papules enlarge centrifugally and neighboring lesions are likely to coalesce. Usually by the time medical advice is sought numerous round or oval, sharply defined patches, ranging from 1 to 5 cm in diameter are found scattered over the limbs. The eruption may be sparse, diffuse or generalized. When a scale is scraped off torn tips of hypertrophied and inflamed papillae are exposed, and minute droplets of blood ooze out, the "bleeding points" typical of the disease. Central portions of some patches may heal so that circinate and arcuate lesions result. The lesions are gen-



Figs 1154-1156.—Fig. 1154 Patches of inveterate psoriasis, forearm. Fig. 1155: Acute psoriasis appearing postoperatively in the abdominal scar of a cesarean section. Fig 1156 Psoriasis of the palm (unusual)

erally dry throughout their course. Itching is generally not a significant complaint although it may be and the anogenital lesions especially are the ones which itch and when fissured, give rise to pain.

The patients are remarkably healthy looking individuals, as a rule and are not ill with their disease excepting those with arthritic accompaniments. Psoriasis is "the disease of healthy people" it has been said.

The eruption may perhaps disappear in the summer to reappear in the winter or spring (Madden MinnM 22 381 1939). If the patient experiences



Fig. 1157.—Psoriasis, showing lesions of long standing. (Dr Howard Fox.)



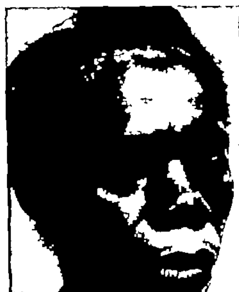


Fig. 11[illegible].—Psoriasis of the scalp in a full-blooded Negro (Dr [illegible] Cannon.)
Fig. 11[illegible].—Psoriasis of scalp in Negress. (Dr O G. Costa.)

some serious intercurrent disease such as typhoid fever the eruption may practically disappear for a time only to reappear as strength is regained.

Although psoriasis is usually slow in its development and chronic in its course it occasionally develops acutely with a more or less widespread, generalized eruption. This often exhibits a preference for cicatricial and bruised or scratched areas, as Small (EdinMJ 25 51 1921) and others have demonstrated

The scalp manifests discrete patches a difference from seborrheic dermatitis. Hair loss does not result. Occasionally the disease is confined to the scalp or is so limited in distribution for a number of years. The palms and nails are sometimes attacked but the backs of the hands and fingers usually escape The hands alone may however manifest the eruption, which can then be identified best by biopsy (Caro and Senear ADS 56 629 1947) Involvement of the palms in 15 cases was the subject interesting to Samitz and Albom (ADS 64 199 1951) On the face or scrotum psoriatic lesions may





Fig 1160.—Oil psoriatic lesions of bizarre configuration.
Fig 1161 —Psoriasis in a Negress. (Dr Isaa R Pels.)

give rise to redness, swelling induration and pain the usual scales being absent The nails show alterations in about half the cases manifesting pitting changes in color onychauxis onychorrhexis and erosion (Crawford ADS 38 583 1938) see p 1370 Otitis externa (p 888) may be psoriatic and extension into the canal may eventuate even in involvement of and damage to the tympanum (Lastinsky DWchr 111 1103 1940)

Once established the disorder may be expected to persist with remissions and intermissions for many years. On disappearing lesions leave no trace except perhaps temporary unevenness of pigmentation Complete and permanent remission is rare Competent and determined treatment undertaken when the disease is new sometimes seems to cure the patient permanently This occurs I should say in possibly one-fourth of my cases.

Koebner Phenomenon —During acute eruption the skin is vulnerable so that the appearance of a lesion is likely to be incited by an injury accidental or experimental which must affect the papillary layer not merely the epithelium.



Fig. 1142.—Psoriasis affecting soles. (Dr Royal M Montgomery.)

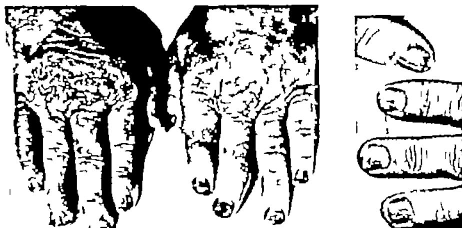


Fig. 1143.—Arthropathic psoriasis.
Fig. 1144.—Psoriasis of nails.



Fig. 1145.—Psoriasis of nails.

As a lesion enlarges, the central part tends to undergo resolution. Within the cleared central region, experimental injury fails to incite new eruption, a refractory state noted by Bizzozero (AnndeD 3: 510 1932) He concluded that the phenomenon may be considered as allergic reaction to an agent X which may be a germ, while the healed zone within an annular psoriatic lesion is in a state of anergy which might be termed immunity to the unknown agent. Lesions made their appearance in that area of the skin which was subjected to x radiation in the case of Frenzl (DWehn 10 : 1429 1935) Adhesive tape incited the Koebner phenomenon in cases seen by O Donnell (MJAustral 1: 193 1940) In one patient, the pressure of a wrist watch strap apparently inhibited the appearance of the eruption at that site a negative Koebner phenomenon observed Fleck (DWehn 1.3: 1 1 1951)

Aberrant Types—In a study of aberrant lesions occurring in some 15% of typical cases of psoriasis, MacKee and Foster (ADS 34 35 1936) found eczematoid, seborrheal lichenoid pustular intertriginous, papulo-erythematosquamous lichen simplex like nodular lupus erythematosus-like and erythrodermic lesions. Levin and Tolmach (ADS 32 718 1935) reported a case with bullae In atypical cases, enough characteristic lesions are usually present to make diagnosis easy

Unusual linear distribution was seen by Auken (ActaD-V 29: 159 1949) and by Leslie (BJD 63: 262, 1951) Carcinoma developed in a large lesion on a man's back (Hannay ADS 60 430 1949) It is not rare by any means, for multiple superficial basal cell carcinoma (q.v) to appear in an old psoriatic who received arsenic in years gone by (Wright and Friedman ADS 77 0 1953) Amyloid was demonstrated in the excessively rebellious lesions of patients of Isaak (ADS 61 839 1950) While mycosis fungoides may manifest psoriasiform lesions, the concurrence of true psoriasis and mycosis fungoides is exceedingly rare but such cases were described by Fox (J 61: 330, 1913) and by Murphy and Montgomery (JID 11 45, 1949)

Mucous Membranes are seldom involved although Jordan (AfDuS 140 64 1922) Keller (DWehn 75 917 1922) Usher (ADS 28 488 1933) and others have reported a few rare instances. Westphalen (DZtschr 54 402. 1928) saw buccal and lingual lesions which when they occur are superficial, red or leukoplakic sharply outlined and oval somewhat resembling lesions of the moist secondary syphilid. In a psoriatic who died of meningioma, psoriasis was found in the hypopharynx, reported Zak and Cisneros (ADS 58 241 1948) whose bibliography was exhaustive Conjunctival lesions are not extremely rare and may exist alone according to Kaldeck (ADS 68 44 1953)

Pustular Psoriasis is rare although examples have been reported by Wrong (ADS 28 683 1933) Bloom (ADS 32 90 1935) and others. During quiescent intervals, the lesions resemble those of ordinary psoriasis (Ebert ADS 27 933 1933) During the subacute stage they become larger more numerous and at times inflammatory Ephemeral, sterile intraepidermic pustules appear in the plaques. Barber (BJD 42 500 1930) and Ingram (BJD 42 489 1930) first reported such cases from Great Britain.

The similarities and dissimilarities of pustular psoriasis of the extremities with dermatitis repens and acrodermatitis perstans have occasioned extensive discussion see Ellis (ADS 33 963 1936) and Barber (GuysHospRpts 86 108 1936) also recalcitrant pustular eruptions of the extremities, and dermatitis of the hands. One hesitates to diagnose psoriasis if the lesions, pustular or not are only on the hands and feet

In the treatment of pustular dermatoses, I agree with Barber in stressing the need for eradicating focal infection. Gaul (NYSJM 36 1219 1936) suggested that the cause of pustulation may be associated with fatty infiltration with mineral oil, which he demonstrated by spectroscopy in the lesions. Psoriatic lesions, being inflammatory may serve to filter from the blood any organisms happening to be there because of the existence of focal infection. thus process perhaps leading to the development of pustulation.

Psoriatic Exfoliative Dermatitis (Erythroderma Psoriaticum)—In rare instances psoriasis becomes universal. In the 18 cases of Goeckerman and O Leary (J 99 2102, 1932) precipitating causes appeared in 14 patients

to be arsenic internally or irritating drugs externally or both intercurrent infection in 3 and pregnancy in 1 Sex and nationality seemed not etiologically significant while 8 cases were associated with some degree of arthritis. The course tended toward stubborn chronicity but Goeckerman and O'Leary obtained satisfactory therapeutic results in 9 cases within 60 days by means of rest and soothing measures. These included colloid and sulfur baths, white precipitate sulfonated bitumen N F., borated ointments calamine liniment, quinine pills of ferrous carbonate U.S P., and autoserum. The 12 patients treated with crude coal tar and ultraviolet rays, the method of Goeckerman (BritJPhysM 7 215 1933) responded in 21 days. Lukashev (VrachDelo 18 479 1936) claimed to have cured a patient by means of hyperthermic treatments.

Prognostically further attacks of psoriasis or of erythroderma may recur but an occasional patient may remain practically free for years. In diagnosis, the biopsy is of definite value

Psoriatic erythroderma in preadolescent children may bear a resemblance to atopic dermatitis or pityriasis rubra pilaris. In cases that I studied intensively, no therapeutic effort was availing although tar, ultraviolet, x rays and cortisone and ACTH were tried. An unusual case was reported by Keil and Trosow (ADS 53: 154 1945) comparable with that of Levi (ADS 1 360 1923) wherein small nodules with psoriasiform histologic structure appeared on the extremities in the course of extensive disease Some of these more were in fact basal cell epitheliomas, while others showed only fibrotic granulation tissue surmounted by irregular acanthosis (compare fibroepithelial tumors)

Psoriasis and Arthritis.—The relationship interesting but unexplained was noticed by Alibert in 1822 (Jeghers and Robinson J 108 949 1937) There is close correlation of the exacerbations and remissions of the skin manifestations with the joint symptoms. The arthritis characteristically involves both large and small joints, with especial severity in the terminal interphalangeal articulations. Psoriasis may exist for many years before the onset of arthritis, which may have its onset during an exacerbation of the cutaneous disease. The joints become swollen, warm and painful.

The association was present in 8 of 1,400 cases of psoriasis reviewed by O'Leary (PSMMC : 90, 1937) An incidence of psoriasis in 8.5% of cases of atrophic arthritis was quoted by Frank and Wallace (JMilitSurg 91: 199, 194_) The psoriasis was severe and unresponsive to therapy in the cases of Gussman (DelibCongrDermatI t rnat 2: 659 1935) who found by roentgenographic studies that the cartilages underwent absorption, the joint spaces narrowed, and exostoses appeared, changes comparable with those of gonorrheal arthritis. Barber (BMJ 1: 300, 1935) remarked that the nails of arthritic fingers show more psoriatic pitting than nails of fingers the joints of which are not affected. In 15 cases of arthropathic psoriasis nail disease preceded joint disease, reported Sherman (JBoneJointSurg 34 A: 831 195_), who did not observe correlation between exacerbations and remission of skin and arthritic lesions. Nonpsoriatic arthritis is less responsive to ultraviolet irradiation therapy than psoriatic (Ebert and Otsuka: ADS 48 324 1943) Rheumatoid arthritis with psoriasis is less responsive to aurotherapy than nonpsoriatic arthritis (Hagan and Tyson: AnMed 1: 252, 1946) Of 543 cases of psoriasis, 37 had arthropathy which was seen only in the severe and moderate cases, never in the mild cases, reported Leczinsky (ActaD-V 28: 483 1948)

The association between psoriasis and arthritis is casual not specific in the opinion of Madden and Karon (ADS 67 66 1953)

Etiology.—The cause of psoriasis is not known. I have seen no evidence that it is at all infectious. It is a common disease The incidence in the American public amounts to about 1 person out of 500 (Sutton ADS 58 740 1948 Bereston ADS 62 716 1950) An incidence 7 times this great was reported among psychiatric patients by Forssman (ActaD-V 27 492, 1947) Statistical studies by Lane and Crawford (ADS 35 1051 1937) showed that psoriasis comprised 6% of the dispensary dermatoses with an average age at onset of 20 years and an incidence 5 times as great in overweight as in underweight individuals. Some 60% of the patients were better in the summertime but 14% of them were worse One third of the patients complained of itching The familial incidence was 26%

Familial incidence occurs in about 30 per cent of the cases, and inheritance is a factor (Lerner JID 3 347 1940) The appearance of the disease at different ages in identical twi s was observed by Mayr (DWehn 100 569 1938) Genetic studies by Steinberg et al. (AmJHumanGenetics 3 267 1951) were, I think, inconclusive

Cases similar to seborrheic dermatitis occur Many investigators believe that psoriasis must be caused by a parasite Wachowiak et al. (ADS 19: 713, 1929) found monilia much more frequently in scrapings and feces of psoriatics than of normal persons. Torrey and Schwartz (ADS 26 7 193_) were unable to prove a relationship with floral variations in the gut. Schwartz et al. (ADS _3 70 1931) concluded that o evidence has yet been found which would indicate any connection between the types of bacteria that vegetate in the human intestine and the development of psoriasis. Numerous organisms ha e been discovered by various observers, but none has as yet been isolated that fulfills Koch s postulates. There ha appeared, to my knowledge no confirmation of the fi ding by Andrezej (AnndeD 1 1 , 1947) of a filamented organism grown from psoriatic scales and from dental calculi and tonsils of psoriatic patients, which he named *Actinomyces lepraeiadit* and from colonies of which he made a vaccine which in 1:1000 dilution induced positive skin reactions in significant proportions of psoriatic patients but not in controls.

While it is not probable that focal infections of the teeth and especially of the ton sil are important etiologic factors, yet when present their eradication perhaps hastens the disappearance of the eruption u der the usual methods of treatment.

Defective li er function has been suggested as a possible ca se, and defective fat *metabolism is hypothesized (Grütz and Burger: KlinWehn 1_: 373, 1933)* but Lewis and Zugerman (AmJMedSci 201: 03, 1941) detected no significant changes in fat toler a ce tests. The influence of lipotropic therapy using soybean lecithin was onspecific in the experience of Gross and Kesten (NYSJM 50 2083, 1950) Dodds et al. (BJD 81: 1_, 194) and Mendora and Orbaneja (abs J 132: 818, 1946) also found no blood fat abnormal ties Yet some psoriatic prisoners of war cleared during the starvation regime of their imprisonme t duri g World War II; others, however became worse in prison No conclusion can be drawn regardi g the etiologic influence of starvation from this ex perience believed Simon (JID 1 : 285 1949) Extreme restriction of diet with respect to caroten a d v tamin A cleared or improved several patients of Hoffmann et al. (NEngJM 236 933 1947)

Hypotheses regarding the psychogenic origin of psoria is were *explored by* Bolgert and So lé (SemHôp 31 1201 1955) Attack of the dermatosis were freque tly precipitated as we have all observed by psychic disturbances of various kin ls.

I have been impressed with the frequency with which the psoriatic shows a need for iron as determined by testing the mean corpuscular hemoglobin con centration and by the seeming benefit of including iron by mouth and vitamin B_{12} by injection in the therapeutic regimen. Yet laboratory tests have been disappointingly unrevealing (Madden MinnM 22 381 1939 Madden and Barthell JID 9 125 1947) *In psoriasis* there are significantly lower acid and iodine numbers of the ether-soluble material from the normal areas of skin than from control individuals and the surface fat of psoriatics has a lower than normal ratio of esterified cholesterol to total cholesterol (Rothman ADS 62 814 1950) Reactive hyperemia is positively deviated from the normal threshold observed Millberg (JID 9 31 1947) who felt that this fact suggests that the causative factor must be blood borne

Pathology—The inflammatory process probably begins in the papillary layer *of the dermis changes in the* epithelium being secondary The Malpighian layer is thickened, but only in the interpapillary regions. Vascular changes and cellular extravasation are more pronounced in older lesions. Cellular infiltration is greatest in the vicinity of coil gland ducts and hair follicles and consists for the most part of lymphocytes and small round cells. Wandering cells and microabscesses of Munro (AnndeD 29 961 1898) occur among the epidermal cells overlying tips of papillae. Linear air spaces in the parakeratotic horny layer account for the silvery appearance of the scale (Burks and Montgomery ADS 48 479 1943) The abundance of melanophages with silver reducing granules in the basal layer *of the* epidermis was remarked by Lovell (abs BJD 60 427 1948) who called attention also to the new formation of collagen in the dermal papillae of active psoriatic lesions. Lipomelanotic reticulosis may occur in extensive chronic cases affecting the brunette skin Abnormalities were found histologically in seemingly normal skin of psoriatics by Kortanysher (abs ADS 40 813 1939) and by Madden (ADS 44 655 1941) Both punctate and leukopathic onychial

changes in psoriasis are due to wavy layers of parakeratotic defective onychization analogous to the typical skin changes (Alkiewicz B-JD 60 195 1948)

Diagnosis.—The eruption is usually characteristic. In some cases, how ever psoriasis might be mistaken for seborrheic or contact dermatitis, syph ilis, tinea corporis, lichen planus or lupus erythematosus.

Seborrheic dermatitis lmost invariably comme ces on the scalp a dandruff and travels down the medial line of the body The scalp i involved diffusel rathe than discretely as in psoriasis. The scales are greasy and bro n The axillae d other flexures



Fig 1106—Psoriasis, histology A—Early lesion with typical parakeratosis, papill ry elongation and superficial inflammation B—Old lesion, thick, acanthotic nd parakeratotic, with ma ked elongation of dermal papillae, over the tips of which the epidermis is thin

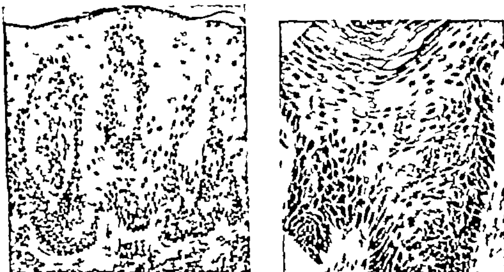


Fig. 1107—Early psoriatic lesion, with acanthosis and papillary edema. (Dr Herman Pinkus)

Fig. 1108.—Psoriasis: microabscesses in the epithelium. (Dr Stuart Way)

ar l kely to be involved, and there may be some te dency to oore. Dermatiti vene ta f rs the flexural surfaces is t harply ci cumscribed, is oft n moist, and is itchy Papulosquamous syphilids are composed of small lesion which come out i crops, do ot exhi it predilection f r xtenso surf ces, are infiltrated and polymorphous, and in the genital gluteal and axillary region ften become abraded and m cerated. Concomitant sign are usually prese t such as palpable lymph nodes, bon pains, mucous patches, and positi e STS Squamou syphilids generally present lesions few in number and asymmetric in distribution They re crusted rather than scaly are lik ly to involve the face or the palms are often circinate or serpiginou in outline give rise to atrophic scarring a d are accompanied by positive serum reaction. In tinea the absence of mother-of-pearl-like

scales, the distribution of the lesions and the demonstrable presence of fungi render differentiation easy Lichen planus attacks flexural surfaces and gives rise to only slight scaling Its lesions are violaceous in color and usually itchy Individual papules are angular and discrete Bleeding points characteristic of psoriasis are absent. In lupus erythematosus, infiltration is less marked, scaling is slight, demarcation is less sharp, and there is usually scarring In disseminated lupus erythematosus, facial lesions may resemble those of psoriasis but body lesions are erythematous or erysipelas-like and constitutional symptoms of some severity are present

Prognosis—It is ordinarily not difficult to clear an attack, but freedom from recurrences cannot be promised Lesions which have existed only briefly are more amenable to treatment than those of long standing Psoriatics do better in a warm dry sunny climate When psoriasis was treated efficiently within one year of its onset its eradication remained permanent in 21% of the cases seen by Romanus (AnndeD 4 361 1946) permanent cure was obtained in 8% of those who had suffered the disease for more than one year It is common knowledge among experienced clinicians that at least some cases are thus cured, and the pessimism of prognosis should not be black.



Fig 1100—Pustular psoriasis intraepidermal pustule filled with leukocytes, and perivascular inflammation localized beneath it (Miller ADS 50 678, 194)

Pregnancy as it relates to activity of psoriasis was investigated by Gruneberg (Hautarzt 3 155 1952) no effect was noted in 124 pregnancies, while in 118 the dermatosis improved or disappeared during gestation.

The development of carcinoma in patches of psoriasis has been noted by *Hovelborn* (*DWehn* 101 858 1935) and Charache (ADS 38 241 1938) See Carcinoma etiology arsenic

Treatment.— Psoriasis is the disease of specialistic frustration (Murrell and Murrell SouthMJ 40 355 1947) While cure cannot be promised, diligent effort and persistence until all lesions are eradicated are to be encouraged. Sometimes the disease does not recur after complete clearing has been attained The psychologic aspect must not be neglected for most patients are at least as discouraged as their physician Watch the *tempo* of the disease advised the Murrels soothe the acute and push the chronic vigorously The patient benefits from hygienic living adequate rest and appropriate attention to concomitant ailments, including nutritional and hormone balance and the elimination of foci of infection.

The best security against relapse is the completest possible removal of all remnants of the disease (Morris BMJ 2 1328 1954) quoted by Ingram (BMJ 2 893 1954) in an interesting essay in which he accepted the view that emotional stress is an aggravating influence which was well expressed by Frank (AmPract 5 872, 1954) The tragedy of psoriasis is most often the patient s attitude

External remedies are essential, and internal agents are only occasionally required. I doubt that any medication given by mouth or injection has been discovered which alone is effectual or as an adjuvant possesses dependable value see Niedelman and Horoschak (ADS 57 271 1948) Mild cases respond promptly and the eruption can be removed in from 2 to 6 weeks mod erate cases require from 1 to 3 months, while extensive and long-standing cases are obstinate

Internal therapy is adjunctive and certainly at times, at least moderately rewarding Yet it is true that No dermatologist would expect to clear up the eruption with systemic treatment alone (Edit BMJ 2 836 1954) From the dietary standpoint it would seem fitting to restrict excessive alcohol coffee tea and animal fats.

Arsenic in the form of Fowler s solution o sodium cacodylate is a time-honored in ternal remedy now practically obsolete Arsphe amine and the antibiotics are valueless.

The cytotoxic drug Aminopterin, i a dose of 0.5 mg daily f r 12 days, cleared or impro ed perh ps 80% of the patients reported Rees et l. (AD 72: 133, 1955) It i a dang rous drug but its toxic—as well a any beneficial—effects are neutralized by a few intramuscular i jections of citrovorum f ctor 3 mg daily Its pharm cologic action may be due to its ability to depress epithelial proliferation by i terfering with n clei cid synthesis. The status of this method of treatment was, in 1955 purely experimental.

Quantities of vitamin D were given by Krafka (JLab&ClinM 21 1147 1936) and by Coder and Zon (PHRpt 5: 1590 1937) who reported helpful effects in 15 cases, 1 of which was arthritic; anorexia, nausea, malaise d bladder irritation were among the toxic ymptoms. Brunsting (PSMMC 13: 290 1938) reported some benefit in 19 cases given 100,000 u its per day and did not poison any of them. It was chrysarobin, not vitami D that helped the patient discussed by Abramowitz (ADS 40: 954 1939)

Riboflavin gi en both i tram scul rly and by mouth was thought to be frequently markedly beneficial by M ynard (JID 18 303, 1952)

In cases of psoriasis with arthritis, phenylb tazone wa given by Kuzell t al. (J 149: 729 1952) who reported that in 6 of the 8 patie ts th skin lesions disappeared and the arthropathy responded fai ly well. Vit min B_{12} i doses of 1000 μg appeared helpful n the experience f R edemann (ADS 69: 728 1954)

Many other remedies, including foreign protein utohemotherapy all varieties f vitamins, sarsaparilla xtract (Th rno : NEngJM 227: 118 194. Saunders: ADS 50 23, 1944) soybean lecithin (Gross and Kesten: ADS 47: 159 1943) lipocal (Stewart et al.: JID 1 1939) salicylates, bismuth, antimony colloidal manganese (Niles: NYS JM 37: 293, 1937) and gold, have been tried and varyi gly assessed. I d not use them; see Madden (J 115: 838, 1940)

Undecylenic acid, i troduced by Perlman (J 139: 444, 1949), underwent a remark ble vogue. The drug was first given to patients with ti ea capitis, in whom it provoked prof se desquamation of th scalp. Therefore Perlman said, he tried it in psoriasis, in which the amazing benefits anticipated f llowi g his report were ot substantiated by other observers. Exfoliative dermatiti following the use of the drug in one patient and hemorrhage from a peptic ulcer in another were reported by Behrman (J 141: 407 1949) It afforded no superiority ove controls in the experience of Goldberg (ADS 61: 661 1950) a d Guy (J 143 761, 1950) I consistent results were obtai ed by Wrong (CanadMAJ 63 543 1950) It wa adjudged worthless or even harmful by Hatt er and Rodin (J 146 1113, 1951) Its history is reviewed t illustrate the fashions and fancies of Medici e which can i retrospect and detachment seem a recreation as well as a science art, mistress or business, according to one mood.

Thyroid extract is helpful to any patient who is thyroid deficient, regard less of his other troubles, which may include psoriasis. Low fat diet is of dubious value (Madden ADS 39 268 1939) The eruption in a hypothy roid psoriatic may prove recalcitrant until thyroid is given.

Cortisone and ACTH have limited value in treating psoriasis. Interest ingly Grüneberg (MünchMWchn 83 561 1936) reported benefit from in

jections of adrenal cortex extract given concomitantly with topical therapy The eruption in a patient undergoing exacerbation may quiet down when cortisone is given Extensive cases under intensive treatment may yield with less recalcitrance under its influence The hormones are no panacea and sometimes fail to influence the disease. It was while ACTH was being given that the patient of Cohen and Distelheim (JID 17 61 1951) developed erythroderma, which faded after the drug was withdrawn In psoriasis with atrophic arthritis cortisone offers the greatest benefit (Sherman B&JSurg 34-A 831 1952) although palliation welcome as it may well be is all that one may expect

Quinacrine helped pustular psoriasis in cases reported by Cormia and Noun (ADS 68 337 1953)

External Applications.—Reducing agents such as chrysarobin, dihydroxyanthranol coal tar ammoniated mercury and betanaphthol are efficient In mild cases the lesions can often be made to disappear under the action of the official ointment of ammoniated mercury alone or reinforced with from 2 to 5% coal tar or salicylic acid and applied night and morning Ointments are best applied with a stiff brush. Chrysarobin is the most effective agent It is potent provoking erythema and even vesiculation like sunburn, and its use entails dangers of conjunctivitis, ocular damage and toxic nephritis.

R Chrysarobin		4.0
Petrolatum	to	30.0

Sig Twelve per cent chrysarobin in petrolatum. Rub in b.i.d. *Avoid eyes with care* [This irritant is promptly counteracted by applications of 1:3,000 aqueous solution of potassium permanganate.]

Dreuw s formula is a popular one

R Chrysarobin		
Oil of birch tar	of each	8.0
Salicylic acid		4.0
Green soap		4.0
Petrolatum	to	60.0

The combination is of no greater value than simply chrysarobin in petrolatum

Dihydroxyanthranol acts like chrysarobin and is used in strengths of from 0.5 to 2.0% prescribed as Anthralin ointment (Becrman et al. J 104 26 1935)

The patient unwilling to pay the price in time and effort will not obtain the benefits that can be obtained.

To secure best results the patient must give himself up to treatment The ointment is thoroughly rubbed into the patches twice daily and the treatment is continued until the skin around all of the spots has become considerably inflamed Five per cent crude coal tar in lanolin and petrolatum may then be substituted for a few days After a bath the entire surface is inspected The remaining traces may be eliminated ordinarily by means of tar ointment

Chrysarobin 3% in chloroform, is a remedy of considerable virtue being not so messy as the ointment It must be pushed by repeated applications until the skin becomes swollen and sore though blistering should be avoided A patient requires instruction until he becomes familiar with the chemical. Anthralin, 1% in chloroform is similarly efficacious.

Psoriasis of the scalp is usually treated with an ammoniated mercury salicylic acid salve supplemented by frequent shampoos Carbowax 1500 being easily washed out is a good vehicle here. Given to an intelligent patient chrysarobin may be used on the scalp with excellent effect although it is dangerous to the eyes.

Psoriasis of the nails is exceedingly obstinate Ammoniated mercury ointment alone or combined with salicylic acid, is helpful. Roentgen therapy

is valuable here Popp and Addington (Radiol 36 98 1941) would direct the beam at the whole hand and wrist including the tips of the fingers.

ULTRAVIOLET IRRADIATION —Goeckerman (NoWMed 24: 229 1925 ADS 24 446 1931 BritJPhysMed 7 215 1933) used ultraviolet light and crude coal tar ointment

℞ Crude coal tar	2.0-6.0
Lanolin, to mix	
Zinc oxide	30.0
Petrolatum	to 120.0
Sig: Tar ointment, f r pso iasis as directed.	

This is rubbed in firmly left on for 24 hours, and then wiped off with mineral oil, a brown stain being allowed to remain purposely The *entire body* is exposed to ultraviolet light beginning with exposures that avoid sunburn. Daily exposures of conservative duration are lengthened rapidly as tolerance increases. Gradual tanning is the object. If natural sunshine can be used for whole-body tanning it is preferable

Goeckerman s method is well standardized and effective as attested by Bigham (BMJ 2 692 1941) and by Brunsting (JMichSMS 42: 546 1943) It is less effective in nummular psoriasis of recent origin and in exfoliative cases (O'Leary CanadMAJ 48 34, 1943) An ambulatory modification was used by Keim who prescribed tar in a cetyl alcohol emulsion base for evening use a tar bath in the morning and a daily visit to the physician s office where liquor carbonis detergens is applied and ultraviolet light administered. The patients of Ellis et al. (JID 10 455 1948) did well on daily paintings with liquor carbonis detergens whether ultraviolet light was or was not used.

Instead of plain coal tar ointment, I frequently prescribe an ointment containing 3% coal tar and 5% ammoniated mercury, using Carbowax 1500 as the vehicle One may apply this to the scalp at night shower in the morning and be not too messy in appearance the next day It is essential to treat the scalp with vigor and determination the disease sometimes seems to center there and disseminate from that region

ROENTGEN THERAPY has great value in psoriasis of the nails and scalp and also in promoting the disappearance of thick, rebellious lesions. Small doses, such as 75 r suffice and enhance the effects of other efforts made simultaneously Precautions must be taken with respect to cumulative dosage and to dosage of large areas with deleterious effects on hematopoiesis. X ray therapy of the scalp may be administered with impunity and great benefit in some cases. An effectual dose is 75 r given by the 5-point technic as in an epilation for tinea. I have never caused alopecia by doing this at intervals of 2 weeks to a total dose of 300 to 400 r

See Pollitzer (JCutD 27: 483, 1909) etiology favored microbic hypothesis, diet worthless Schamberg (JCutD 27: 494, 1909) etiology unknown, review, Ketron (JCutD 32 216, 1914) dark-field microscope in exploration negative Fox (JCutD 33 478, 1915) autoserum therapy combined with chrysarobin Fordyce (JCutD 33 498, 1915) lues case; Perry (BostonM&SJ 74: 274, 1916) horse serum therapy; Winfield (JCutD 34 441 1916) 6 cases which followed tonsillar infections Pusey (JCutD 37 [illegible] 1919) queer treatments tried by one patient; Brock (Strahlentherapie 11 2, 1920) x-radiation of thymus Wagner (DWchn 73 [illegible], 1921) pathology; Jameson (ADS 4 [illegible], 1921) no changes in blood urea; Foerster and Fox ster (ADS 4 [illegible] 1921), favorable experience with x ray therapy of thymus, Brock method; Sutton (ADS 4 [illegible] 1921) chrysarobin treatment Kilroy (ADS 4 [illegible], 1921) entertaining aspects of etiology, [illegible] (JID 34 [illegible], 1922) intravenous sodium salicylate [illegible] (JID 36 [illegible] 1923) histology and diagnosis Schamberg (J [illegible] 1924) the known and unknown about psoriasis; Maloney (ADS 9 752, 1924) sodium salicylate therapy; [illegible] et al (BullSocfrancD [illegible] 1926) insulin therapy; Toomey (JID 40 448, 1926), gold therapy, favorable experience; Sutherland and Frost (ADS 22 [illegible], 1930), injection of patient s scales suspended in alcohol Maschkilleisson and Abramowitsch (DWchn [illegible] 1614 1931) ultraviolet used prior to chrysarobin applications diminishing irritation, hastening cure Nordin (ActaD-V 15 221 1934) pustular and arthropathic case autopsy Hosh (AmJRoentg [illegible], 1934) irradiation of spine; Tauf and Staud (ADS 30 [illegible] 1934) spectrometric demonstration of [illegible] in lesions Grütz (DeutschMWchn 60 [illegible] 1934) low-salt diet; [illegible] (NewJerseyMSJ [illegible] 1935) intravenous [illegible], Pamla and Maplestone (IndMGaz 70 [illegible], 1935), [illegible] therapy with tissue filtrate; Barber (DeltbCongrDInternat IX 2 [illegible], 1935) pustular psoriasis, relation of tonsillitis; Thurmon (NEngJM [illegible], 1935), intravenous sulfur, Kartamischew (DWchn 102 [illegible] 1936), hypnotic therapy; Detect (ADS 33: 327 1936) historical review Callaway (ADS 35 [illegible], 1937), Sirod, an organic mercurial proprietary (see J 108 [illegible], 1937); Oliver and Crawford (ADS 35 1120, 1937) colloidal [illegible]; [illegible] (CanMAJ 63 [illegible], 1938), Haml C; Cortial ([illegible] 1938) lymph nodes, eosinophilia, reticuloendothelial proliferation, pigmentation, Gaté et al. (AnnD [illegible] [illegible], 1938) cholesteremia variable, diet Iacedayl and Ottenstein (Dermatologica [illegible] 16, 1939)

pancreatic function, low fat diet; Wise and Sulzberger (YBD 1940, p. 1), review, Clarke (ADS 41 664 1940) failure of vitamin D Ronzani (abs ADS 46 142, 1942) Lindenberg blood serum virus unconfirmed Venkei (Dermatologica 82 66, 1940) antigen against blood serum of psoriatic patient obtained by animal inoculation of filtrat of lesions Kierland (JID 3 273 1940), nonspecific streptococcus from nasopharynx of psoriatics, Desaux et al (BullSocFrançD 47: 50 1940) increased A/G ratio Gahan (UCutRev 45 472, 1941) review Goldfarb (ADS 43 530 1941), vitamin C and citrin therapy Ayres, Becker Chargin, Cornbleet, Fox, Madden, O'Leary (JID 4; 399 ff, 1941), methods of treatment Walsh et al. (JID 4 58, 1941) lipocaic helpful Wernsdörfer (MünchMWschr 88 965, 1941), eosin added to chrysarobin ointment, for photodynamic effect, then ultraviolet Saunders (N WMed 41 135, 1942) effective external treatment Downing et al, (ADS 45 1128, 1942) lipocaic worthless; Goldfarb (NYSJM 44 1111 1944) citrin Swartz (NEngJM 233 206 1945), autogenous Str faecalis vaccin LeWinn and Urbach (ADS 51 398, 1945) high vitamin C, low K, intake and adrenal cortex extract Schonberg (Oh MJ 42 254, 1946) effective external treatment Epstein (JID 8 203, 1947) photosensitizes with sulfonamide, then use tar and UV —dangerous QBIN (J 135 606, 1947) nails Norrlind (ActaD-V 28 571 1948) streptococcus agglutination; Gilg and Perdrup (abs J 140 1266, 1949) urethane useless Klinck (JID 13 261, 1949) gamma globulin perhaps helpful Rothman and McCreary (ADS 60 896, 1949) tobacco juice cured pustular cases Michi (JID 13 1, 1949) phytopharmacologic studies Reuss (ADS 59 72, 1949) chemical studies of serum Perlman and Milberg (J 140 865, 1949) undecylenic acid and reaction hyperemia Barber (BMJ 1 219 1950) hypothesis of etiology in inborn mode of reaction Cohen (MedIllustr 4 409 1950) leprosy of Bible probably psoriasis Ingram (MedPract 224 5, 1950; BJD 64 211, 1952) treatment with anthralin, UV and baths in liquor carbonis detergens, 4 oz to 20 gallons of water; MacKenna (BMJ 2 207 1950) refresher review Nelson (CalifM 74 17 1951) exudative dermatitis from undecylenic acid, Allende et al. (ADS 63 284 1951) D_2 intramuscularly failed, Orbaneja (RevClinEspañ 40: 299 1951), nitrogen mustard cleared some cases Gans (ADS 66 598, 1952) etiology Huff and Taylor (ADS 68 385, 1954) vascular dysfunction indicated by plethysmograms of fingers Siemens (ActaD-V 34 208, 1954) favorable effect, "co-reaction," of untreated patches when remainder of psoriatic eruption was treated Solomon et al. (ArchPhysMedRehab 36 74 1955) Goeckerman tar and UV therapy Morris (AD 71 626, 1955) Koebner phenomenon at scratch test sites Buskind (JID 23 348, 1956) psoriatic lesions anhidrotic until clinically healed Benedek (ActaD-V35 Supp 2, 1955) "specific" vaccine.

THE RESISTANT MACULAR AND MACULOPAPULAR SCALY ERYTHRODERMAS

Colcott Fox and MacLeod (BJD 13 319 1901) in describing particularly parakeratosis variegata suggested the above designation for an ill-defined group of chronic dermatoses many of which are clinically suggestive of a double triple or quadruple combination of psoriasis lichen planus, seborrheic dermatitis and early mycosis fungoides. The various eruptions are generally of slow evolution, with pink or reddish, circumscribed, sharply defined patches which range from ½ to 6 cm. in diameter and are scattered irregularly over the body

Parapsoriasis.—Wise (NYSJM 28 901 1928) preferred to keep the old names which are legion, until basic understanding is available For teaching purposes he placed the lot under the title Parapsoriasis and, modifying the classification of Brocq arranged the types as follows

- (A) Guttate
  - (1) Parapsoriasis en gouttes (Brocq)
  - (2) Dermatitis psoriasiformis nodularis (Jadassohn)
  - (3) Pityriasis lichenoides chronica (Juliusberg)
- (B) Retiform
  - (1) Parapsoriasis lichenoide (Brocq)
  - (2) Parakeratosis variegata (Unna, Santi and Pollitzer)
  - (3) Lichen variegatus (Crocker)
- (C) Plaque
  - (1) Parapsoriasis en plaques (Brocq)
  - (2) Erythrodermie pityriasique en plaques disséminées (Brocq)
  - (3) Xantho-erythrodermia perstans (Crocker C J White)
- (D) Parapsoriasis atrophicans (Kreibich)
- (E) Pityriasis lichenoides et varioliformis acuta (Habermann)
- (F) Mixed

These may be described under the following headings (following Wise)

Parapsoriasis Guttata.—Lesions are small pale red or reddish brown and slightly infiltrated with dry adherent scaling If the scales are scraped off a red purpuric spot appears, but no bleeding points. There is close clinical resemblance to guttate psoriasis This group includes A 2 and A 3. Pityriasis lichenoides chronica of Juliusberg (HandbHuG 7 311 1928) included by Wise within the designation parapsoriasis guttata is pruritic,

Fig 1170.—Pityriasis lichenoides t varioliformis acuta. (Dr Paul Gross.)
Fig. 1171.—Pityriasis lichenoides et varioliformis acuta. (Drs Wise and Sulzberger.)



Fig 1172.—Parapsoriasis arioliformis, 6 months' duration. (Drs. Wise and Sulzberger.)

enduring unresponsive to treatment and otherwise not different from the acute form, which was thought to be a variant of the chronic by Gross (ADS 12 33 1931)

Parapsoriasis Papulata.—The lesions are more papular infiltrated and advanced, and they scale less Some have central depressions and glistening surfaces and resemble lichen planus. They are usually scattered, especially over trunk and extremities, and may be described under the headings (1) lichenoid (2) nodular (3) reticular and (4) striated. This group includes B-2 and B-3

Parapsoriasis Maculata.—The lesions are macular and disseminated or widely distributed. They are not infiltrated Scaling is faint or absent. The color is yellowish salmon, purplish violaceous, reddish or reddish brown. The surface is often wrinkled shriveled or faintly atrophic. The configuration may be round, oval striate reticulate or banded. Lesions occur especially on

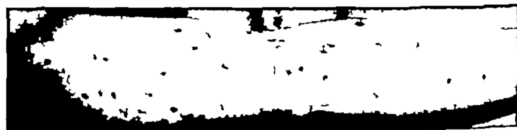


Fig. 1173.—Pityriasis lichenoides et variol formis acuta. (Drs. Wise and Sulzberger)

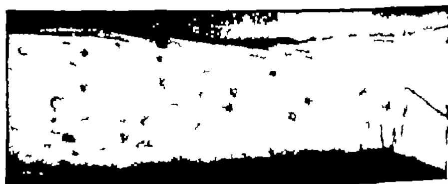


Fig 1174.—Lesions lik those of pityriasis lichenoi les et varioliformis cuta in woman with calcified axillary nodes negati tubercul reactivity nd a positi histoplasmin test. The eruption d sappeared after a few injection of gold sodium thiosulfate.

the trunk and thighs. They resemble lesions of seborrheic dermatitis, lepra or early mycosis fungoides. Cases may be described as (1) discoid, or in plaques, (2) reticular and (3) xanthous. This group includes C-2 and C-3.

Parapsoriasis Atrophicans (Kreibich AfDuS 144 476 1923) —The elementary lesion was a pinhead-sized, opaque white vesicle containing neutrophile leukocytes, surrounded by a zone of yellowish red hyperemia On drying a thin crust formed for the vesicopustule being intraepidermal, was accompanied by chronic destructive inflammation of the dermis. Healing occurred with undergrowth of new epithelium beneath the crust Fresh lesions persisted in appearing on the breasts, back and arms. Atrophy succeeded the healing

Parapsoriasis Varioliformis (*Pityriasis lichenoides et varioliformis* of Habermann DZtschr 4 42 1925 described but not so named by Mucha AfDuS 123 586 1916) —Senear and Oliver (ADS 23 12, 1931) noted The outstanding feature is an eruption of generalized character with varying eruptive manifestations, the most characteristic of which is a papular lesion

with a tendency to crusting necrosis and hemorrhage. Pigmentation and varioliform scarring follow the disappearance of some of the lesions. The general health of the patients is unaffected. No etiologic factors have as yet been determined. There is no evidence that the disease is contagious. In different cases, and at different times in a single case the eruption has borne a striking resemblance to that of papular syphilis and pityriasis lichenoides chronica while in some instances it has simulated varicella, pityriasis rosea, psoriasis, and lichen planus.

Vesicular hemorrhagic and necrotic lesions on the palms and soles were striking features of the eruption in cases of Wise and Satenstein (ActaD-V 14: 245 1933) while the patient of Wise and Sulzberger (MedJ&Rec 132 331, 1930) had lesions on the palms, soles and eyelids.

The microscopic picture of parapsoriasis varioliformis must be construed as a parapsoriatic process with unusually extensive inflammatory alterations in the connective tissue st ted Almkvist (DZtschr 46: H 3, 4, 19?6) Gross (ADS 23: 83, 1931) after careful study of 3 cases and a survey of the literature, also believed that it belongs in this group. H suggested that the difference between parapsoriasis varioliformis a d pityriasis lichenoides chronica lies only in the degree of the micropathologic changes. Michelson (ADS 35: 11 8, 193?) thought that the disease may be a trichophytid. Pityriasis lichenoides wa described by Ingram (BJD 65 293, 1953) as a self limited disease without serious sequelae to be distinguished carefully from the parapsoriasiform conditions which may proceed to malignant reticulosis.

See Scholtz (ADS 30 631 1934); Greenhouse and R bin (ADS 31 83, 1935) Caccialanza and Dellone (bs BJD 65 436, 1953) review and Italian case of Habermann-Mucha disease.

Parapsoriasis Mixta.—This heading contains cases which present features of two or more of the preceding clinical groups. See Riecke (AfDuS 83: 51 205 411 1907; 131: 450, 19?1) reviewing l terature prior to Wise (1923)

Parakeratosis Variegata, the retiform variety of parapsoriasis was discarded by McCarthy (ADS 45: 81, 1942), who believed that modern diagnosis of such cases would result in th ir bei g distributed among th unusual forms of lich n pl nus or among other varieties of parapsoriasis. See Schoch (Dermatologica 78 1 1939)

Parapsoriasis en Plaques Disseminées was actually the early stage of mycosis fungoides in a significantly high proportion of the 31 cases reviewed by Keil (ADS 37 465 54?, 1938) If early mycosis fungoides were surely identifiable, parapsoriasis would be diminished to that extent (see case of Costello and discussion: ADS 41 177 1940), for many cases, especially those which resemble Brocq s *erythrodermie pityriasique en plaques disséminées* are in fact, as Brocq s case proved to be, examples of early mycosis fungoides, the histologic lesions of which are not pathognomonic. Keil believed that parapsoriasis en plaques disséminées, the lichenoid, variegated and retiform varieties of parapsoriasis, and particularly parapsoriasis with transition into poikiloderma all represent phases of a single condition which terminates in mycosis fungoides. Distinction is to be made from pityriasis lichenoides chronica (parapsoriasis guttata) and parapsoriasis varioliformis which are not of this nature.

Dividing the parapsoriasis group into 2 main classes, the pityriasis lichenoides type and the parapsoriasis en plaque type Lapiere (abs BJD 60: 347, 1945; 62: 4 4 1950) was convinced that the forme is never the forerunner of m cosis fungoides, while the latter may be. In the parapsoriasis n plaque type, some cases are actually early mycosis fungoides while others pursue a benign course. When parapsoriasis becomes mycosis fungoides, it does so abruptly Civatte (AnndeD 78: 5 1951) in an rticle reviewi g Brocq s grouping (parapsoriasis guttata, lichenoides, and en plaque) pointed out th t histologically the papule of the lichenoid form is primarily a dermal lesion, and in th guttat form epidermal changes are conspicuous while the dermis is affected only secondarily In both the lichenoid and en plaque varieties infiltration in the papillary layer of the dermis is present and may produce destruction of elastic fibers, the finding of which diff rentiates these diseases from the guttate type of cases. See Montgomery and Bu khart (ADS 46: 672, 194.)

Treatment.—The drugs commonly used for psoriasis and chronic seborrheic dermatitis sometimes prove of service including chrysarobin. Kulchar (UCutRev 40 38 1936) treated 2 cases successfully with dioxyanthranol. In cases which resemble seborrheic dermatitis, treatment of the scalp as for



Fig. 1175.—Parapsoriasis en plaque showing lesions such as may eventuat in mycosis fungoides. (Dr Fred Wise.)

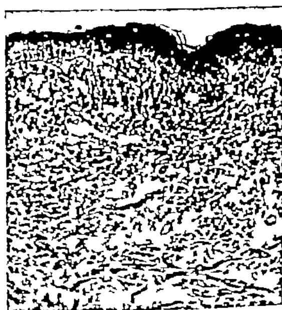


Fig. 1176.—Pityriasis lichenoides chronica, showing pidermal and subepidermal edema, acuolization, and round cell infiltration. (Dr Fred Wise.)

seborrheic dermatitis is necessary. Lassar's paste will cure some cases which chrysarobin simply irritates. The removal of milk and cream from the diet benefited 2 of my cases which resembled psoriasis. Cases resembling lichen planus probably are aberrant lichen planus (q.v.) and should be treated as such. X-ray therapy in doses of 100 r may be quite helpful.

In pityriasis lichenoides acuta 1% coal tar in Lassar's paste, softened with liquid petrolatum, may work well. Ultraviolet light used over the whole body may enhance the effectiveness. In the chronic form, I had success in one case, a woman whose skin tests and chest film suggested that she had histoplasmosis, with gold sodium thiosulfate given intravenously.

Parapsoriasis en plaque proved responsive to calciferol, reported Barber and Erskine (BJD 61: 100, 1949), at least during the time the drug was being given. In 3 of 4 cases, Canizares et al. (JID 16: 121, 1951) also had favorable results with vitamin D.

As in dealing with any chronic dermatitis of undetermined cause, attention should be given to focal infection, anemia, nutrition and hormonal balance. When I say a patient has "parapsoriasis," I mean that he has a rash reminiscent of psoriasis and that I do not know what is the matter with him.

PITYRIASIS RUBRA PILARIS

Pityriasis rubra pilaris is a rare, chronic, sometimes fatal disease characterized by hard, yellowish or reddish hyperkeratotic papules situated at the mouths of hair follicles and coil gland ducts. The nutmeg grater-like appearance of the hairy aspects of the dorsa of the fingers is a classic feature. Coalescence of the papules results in the formation of mildly inflammatory scaly areas, which may be of considerable, even universal, extent. The dry exfoliation resembles that of seborrheic dermatitis.

Synonyms include lichen ruber (Hebra), lichen ruber acuminatus (Kaposi) and lichen acuminatus (Crocker). Devergie (Traité pratique des Maladies de la Peau, 1859, p. 454) described the condition as "pityriasis rubra pilaris," and it has always been known by that name in France. The older Hebra employed the appellation "lichen ruber," and his son-in-law and disciple, Kaposi, later changed this to "lichen ruber acuminatus," mainly to prevent its confusion with lichen ruber planus of Wilson, which is lichen planus. All of Hebra's early cases, a dozen or more, died as a result of the disease, whereas pityriasis rubra pilaris seldom nowadays proves fatal.

This description follows that of Devergie, Besnier and Brocq. The sites of predilection are the backs of the hands and fingers, particularly the first and second phalanges, the extensor surfaces of the wrists and forearms, anterior axillary folds, and the elbows and knees. The characteristic lesions are hard, dry papules seated at the mouths of the hair follicles, each enclosing in its center a dry, lusterless, atrophic hair shaft. *The horny plug extends into the follicle a considerable distance.* The papules are discrete at first but tend to become confluent, involving areas of considerable extent and giving rise to thickened, yellowish-red or grayish-red plaques, which are rough, dry and partially covered with branny scales. Deep folds, and sometimes fissures, form at the joints. The palms and soles are thickened, and the nails may become grayish, brittle and striated. On the scalp the lesions somewhat resemble those of a long-standing dry seborrhea. The hair in this region is not markedly affected, however. The mucous membranes may be involved, with whitish, linseed-sized raised lesions on the palate (Marshall: ADS 66: 626, 1952) simulating lichen planus (Gilchrist: ADS 1: 105, 1920). The skin of the face becomes thickened and inelastic with more or less scale formation. Ectropion of the lower lids may be present. Itching is slight or entirely absent. As usually encountered the disease is accompanied by slight constitutional symptoms, and the general health is unimpaired.

Etiology.—The majority of patients are young adults, although no age from 2 years upward is exempt. The disease used to be reported frequently from Austria and France. Zeisler (ADS 7: 195, 1923) observed 4 cases of



Fig 1177.—Pityriasis rubra pilaris (Dr Howard Fox.)



Fig. 1178.—Pityriasis rubra pilaris. (Dr How rd Fox.)



Fig 1179.—Pityriasis rubra pilaris. (Dr How rd Fox.)



Fig. 1180.—Pityriasis rubra pilaris. (Dr Gusta Riehl.)
Fig 1181.—Pityriasis rubra pilaris, typical on other parts of this woman's skin, resembled lichenoid dermatitis of the vulva. (Dr O G Costa.)



Fig 1182.—Pityriasis rubra pilaris typical follicular hyperkeratotic lesions of the dorsa of the phalanges.



Fig. 1183.—Pityriasis rubra pilaris, lesions of elbows. (Dr D. H. H. Cleveland.)

pityriasis rubra pilaris in one family I (Introduction to Dermatology Mosby 1937 p 189) pointed out that the similarity of the lesions to those of avitaminosis A (q v) is noteworthy these conditions are almost indistinguishable as judged by the literature photographs and photomicrographs. The identity and nature of the disorder were for many years the subject of controversy but the view that it represents nutritional deficiency principally in vitamin A was supported by Jeghers (NEngJM 228 714 1943) Pettler (PaMJ 39 864 1936) Weiner and Levin (ADS 48 288 1943) Large doses of vitamin A help such patients, though this is not the whole story in the judgment of Porter and Golding (BJD 57 197 1945) for liver function is probably deranged (Leitner BJD 58 124 1946) Familial cases were reviewed by Leitner and Ford (BJD 59 407 1947) it being judged that the disease is inherited as a simple autosomal heterozygous condition some of their patients showed defective liver function.

Defective liver function may account for the fact that large doses of vitamin A fail to benefit some patients (Moore BJD 58 17 1946) for tests may reveal gross impairment (Leitner BJD 58 124 1946) In their analysis of 58 cases all but 4 of which improved on vitamin A therapy Kierland and Kulwin (ADS 61 925 1950) divided them into two groups those cases commencing in infancy and those with onset in middle age



Fig 1184 —Section of pityriasis rubra pilaris, showing funnel-shaped, hyperkeratotic follicular plug made of concentric horny layers. Note the marked hyperkeratosis and increase the granular layer the slight perifollicular infiltrat consists largely of lymphocytes (Dr H L Michelson)

Pathology—Th re is pro ounced hyperkeratosis througho t the affected area al though the princ pal changes occu in the lei ity of the mouth of the h ir follicles and sweat orifices. In these local t es thickening i especiall prominent the outer corneous l rs be g those princ pally n lved. There i some canthosis, The papillae are lo gated and filtrated, w th some rou d and mast cells. Liq efaction serosis of the basal la of th epiderm s PRP differs from the pathology of avitaminosis A, ac cord g t Brun ting and Sheard (ADS 43: 4., 1941) while parakeratosis is marked i PRP not n A deficiency

Diagnosis.—The chara t r and localizatio of the lesions, the dry scaliness of the scalp and f th palmar and plantar thickeni g a d the bsence of symptoms are di tincti I psoriasis both the dorsal and palmar surfaces of the hand generally escape the face i seldom in lved, th les on are ot f llicular papules, n l they enlarge by peripheral e t nsion tead f by confluence I exf liati dermatitis there is marked erythem with l ttl o n th ke i g, the scales are large a l papery and the onset is acute, with som att ding const tution l dist rbance I ichthyosis the history alone is usually sufficient to prevent confusion, and the absence of typical papules and redness l distinctive Th red o violaceous color of the lesions in lichen pla o the presence of the typical papules t some stag f the disease and th location and itchi ess should prevent confusion.

Prognosis.—The disease is chronic and persistent, rebellious to treatment, and prone to relapse even after years of apparent freedom. Fatal cases such as were reported by Hebra are rare.

Treatment.—Of the internal remedies, arsenic in the form of Fowler's solution, or sodium cacodylate (Heidingsfeld) thyroid extract (Crocker) mercury (C. J. White) pilocarpine and various tonics have been employed with purported benefit. A balanced and nutritious diet including milk, eggs, liver and green vegetables should be helpful. Locally alkaline or starch water baths are excellent, followed by a bland unguent incorporating from 1 to 3% salicylic acid. Weak tar ointments sometimes prove valuable. Ointments are liable to promote secondary staphylococcic parasitism, with folliculitis, furunculosis and the formation of abscesses. Much benefit has followed the administration of vitamin A in some cases, such as that of Peck and Chargin (ADS 44: 722, 1949). When ACTH was also given, the effects were better than were obtained by vitamin A alone in the 2 cases of Webster and Falk (ADS 65: 685, 1952).



Figs. 1183 and 1184.—Hyperkeratosis follicularis et parafollicularis in cutem penetrans: front view of patient, and closer of the lower back. (Thyresson: ActaD-V 31: 367, 1951.)

HYPERKERATOSIS FOLLICULARIS ET PARAFOLLICULARIS IN CUTEM PENETRANS

Originally described by Kyrle (AfDuS 123: 466, 1916) and reviewed by Arnold (ADS 53: 633, 194) this is a disease of which there are less than a score of cases on record. The original patient was a young woman with an eruption of some 6 months' duration, consisting of polycyclic, hyperkeratotic plaques in the axillae, on the forearms and on the shoulders. Removal of the heavy scales and crusts revealed closely set, discrete crateriform papules a few millimeters in diameter, topped by central depression about mm.

wide and deep. Conic, keratinous pegs fitted into these pits, and their points extended lowanward into the acanthotic epidermis in some instances actually penetrating the basal layer and inciting foreign body reaction in the dermis. An old man with a more extensive eruption, with seborrheic features and elevation of nails by subungual keratoses, was described by Fried (AfDuS 143: 45 1923) Other cases have been seen in persons of various ages with lesions of extensive or limited distribution. Not itchy the eruption resembled avitaminosis A in the old woman seen by Thyresson (Twelfth Meeting Northern Dermat Soc., Oslo 1949 p. 237) and from her entire trunk circular keratotic papules, red or reddish brown and painful on pressure could be detached. The legs were the site of such lesions of from pinhead to split pea size, with central horny plugs in smaller ones and grayish yellow crusts covering larger ones, in the woman 60 years old exhibited by Scott (BJD 61: 1 6 1949)

Pe etration of the epidermis by horny masses, Kyrle s phenomenon, may occur in dermatoses other than Kyrle s, according to Beek (Dermatologica 109 217, 1954) who accepted only 3 cases on record, including 1 of his own as being identical with the original one.

The cause and cure of the disease are unknown.



Fig. 1167—Hyperkeratosis follicularis et parafollicularis in cutem penetrans, the histologic lesion. (Dr Nils Thyresson.)

EXFOLIATIVE DERMATITIS

Symptoms.—Exfoliative dermatitis is the descriptive title given to any desquamating dermatosis of extreme distribution and inflammatory appearance. The class is etiologically heterogeneous, for generalized or universal involvement may be due to diseases of the following varieties, descriptions of which should be viewed from this standpoint

Dermatitis ve enata	Dermatitis of parasitism bacterial or fungous, primary or secondary
Dermatitis medicamentosa	Psoriasis, parapsoriasis, seborrheic dermatitis
Atopic dermatiti	Lymphoblastoma
Lichen simplex, autoeczematization	Combinations of these
Avitaminosis a d hypoproteinosis	
Pemphigus foliaceus	

If one were competent to recognize and deal with the illnesses represented in the foregoing list when the case is an extreme example of its kind, one would have no use for the name exfoliative dermatitis. Yet we are not quite ready to dispense with the traditional descriptions of the two forms of Wilson and Brocq and of Hebra, as follows

Exfoliative Dermatitis (Wilson Brocq) may be either primary or secondary In the primary variety the eruption appears suddenly and may be

either patchy or universal. Pinkish or reddish at first and symmetrically distributed, the affected areas become covered with thin, flaky loosely adherent, grayish or brownish scales. From the volar surfaces the corneous layers are sometimes thrown off in glovelike casts. Nails and hair both may



Fig. 1168.—Exfoliative dermatitis supervening upon chronic dermatitis of the hands with "autoeczematization" in recent months. (Dr Grover W Wende.)

be shed. There is usually little itching although the skin is tender and the patients complain of tension, stiffness, chilliness, malaise and debility. The amount of scaling varies but is profuse and a liter may be exfoliated within each 24 hours. Acute cases exhibit little cutaneous thickening but in long

standing ones infiltration may be considerable. There is no vesiculation or exudation as a rule An outbreak lasts for several weeks or months, and relapses are likely

In the secondary variety the condition follows various scaly affections such as dermatitis venenata psoriasis and seborrheic dermatitis. It is probably often the result of irritant medication in conjunction with defective nutri-



Figs 1189 and 1190 —Exfoliative dermatitis in a Hawaiian, showing universal [illegible] thickening and pigmentation of the skin, and lymphadenitis. (Dr J C W [illegible])

tion Malaise chilliness and fever are common complaints. I have seen a patient with mercurial exfoliative dermatitis develop a fever of 6 F in 6 hours following Merthiolate wet dressings this in fact, was the clue which led to correct diagnosis. Oozing is likely to be a feature and paroxysmal flares with violent itching and distress are observed. Bacterial invasion, impetiginization furunculosis and abscesses may make their appearance especially in the axillary and other hairy regions often as a complication of

the use of ointments, which cannot long be applied safely to these regions even if the skin is normal. Lymphadenitis, leukocytosis, and relative eosinophilia are generally found.

Pityriasis Rubra (Hebra) a rare, chronic dermatitis, is characterized by involvement of the entirety of the body surface, general lymphadenopathy only slight infiltration and pruritus, pigmentation, eventual glossy atrophy and unremitting duration until death ensues. Weakness and emaciation are progressive. The soles are likely to become too atrophic and fragile to support walking Abscesses are common. The patient complains of chilliness, and he huddles beneath the bedclothes. No area of skin is likely to become normal, even temporarily during the course of the disease Hypoproteinemia was extreme and unyielding in an elderly woman I treated in 1954 whose autopsy revealed no hint of the cause of her troubles.

Etiology—Exfoliative dermatitis occurs usually in middle life and prefers males in a ratio of 3 to 1 I believe that many cases commence as banal inflammation, upon which is superimposed dermatitis of contactant intolerance; and this becomes secondarily involved with pathogenic microorganisms. Focal infection may play an important role while anemia hypoproteinemia and lichenification are also significant factors. Diminution of serum albumin and hippuric acid excretion varied paralleling the severity of the disease in 10 cases studied by Bauer (AustralJD 2 69 1953) with special concern regarding liver function, damage to which appeared pertinent to dermatitis. When ACTH or cortisone altered the disease the results of the tests underwent similar alteration. Most cases follow upon the generalization of a preexisting dermatosis noted Wilson (ADS 69 577 1954) of whose 50 patients 28 recovered, 19 died and 3 remained unchanging

Pathology—The papillary bodies are enlarged and elongated and both they and the subjacent dermis are moderately infiltrated with leukocytes. Cellular exudate is greatest in the vicinity of the vessels and around the coil gland ducts. The epidermis is thinned irregularly hyperkeratotic and parakeratotic, and scaling The benign hyperplasia of lymph nodes occurring in exfoliative dermatitis may be accompanied by remarkable melanin pigmentation conveyed to the nodes from the skin lipomelanotic reticulosis.

Lipomelanotic reticulosis is manifested by hyperplasia of the superficial lymph nodes in accompaniment with various widespread, itchy dermatoses. First fully described by Pautrier and Woringer (AnndeD 8: 257 1937), it has been studied by many including Hurwitt (JID 5: 197 194), Robb-Smith (BritMBull 3 172, 1945) Schnyder and Schirren (Dermatologica 108: 319 1954) and Nairn and Anderson (BMJ 1 820, 1955) It may occur in leukemia and in mycosis fungoides (Bluefarb and Webster: ADS 61: 830 1950) The nodes involved are the ones that drain the regions of chronic dermatitis. It is a benign condition, the pigment in the nodes being that which has been removed in a physiologic manner from skin where it has been produced in unusually large quantities.

The effect of generalized dermatitis on skin temperature and BMR was investigated by Mali (Dermatologica 104 19, 1952) The BMR is increased as a rule and energy loss from the skin combines with protein loss, to the disadvantage of the patient

Prognosis must always be guarded. It is never possible to predict freedom from recurrences, and some patients die. Death in the days before antibiotics was generally the result of bronchopneumonia. Death was due to irreversible peripheral circulatory collapse in 4 patients observed by Steiner and Grayson (J 151 1476, 1953) who felt that these fatalities were related to the use of cortisone and ACTH, drugs which, they urged should be used cautiously in minimum effective dosage.

Treatment.—Tonics and generally supportive measures may be recommended. Hospitalization for adequate supervision and elimination of contactant factors is almost indispensable Aspirin is a useful sedative but bromides are not desirable Barbiturates, chloral or opiates if needed are to be used, for the patient must receive palliation (see Pruritus) All the measures for dealing with chronic lichenoid dermatitis (p 876) are appro-

priate elimination of focal infection, assurance of dietary adequacy administration of iron and vitamins, correction of anemia and hypoproteinemia, support of liver function correction of hormonal imbalance utilization of vitamin B_{12} cortisone and, perhaps ACTH Chloride loss in an oozing patient must be replaced. Sodium thiosulfate intravenously had its advocates, but, like calcium, is without virtue in my experience.

In choosing topical remedies one must be certain that intolerance does not exist. Salicylic acid, sulfur mercury tars and even medicinal vehicles are all potential causes of exfoliative dermatitis in certain individuals. Baths *and wet packs, with occasional drying by means of radiant heat and cradles* with lights and the control of secondary infection with Achromycin and the like are measures which are likely to meet with some success. Oily applications must be used with circumspection, for they predispose to staphylococcic complications. Liberal application of bland powder is often beneficial. Sulfonamides may help yet sulfonamide intolerance may cause the disease. Penicillin is remarkably beneficial in many cases, even in the dry type I was *shown by Novy in 1944. The dose should be large and should be given in* courses of 7 to 10 days broken by rest periods. Penicillin has been known to cause exfoliative dermatitis. Benefits of cortisone were conspicuous in cases of West (ADS 65 56 1952) although the drug entails hazards (Steiner and Grayson J 151 1478 1953)

X ray therapy is often of value its extensive use in modest dosage being controlled by studies of the blood

The patient of Witherspoon (ADS 53 506 1946) was not helped until amebae were found in the stools and antiamebic therapy was instituted. Parenchymal changes in the lungs were associated with dermatitis in the cases of Frostberg (abs YBD 1948 p 173) and disappeared as the skin healed.

See Montgomery (ADS 27: 253, 1933) histologic distinction of benign and lymphoblastomatous exfoliative dermatitis, Pool and Wehger (J 103 746, 1934), fatal cases with exfoliation of pulmonary epithelium, sometimes of renal epithelium Banferin (DWchn 60 1337, 1934), Wilson Brocq case Müller (MünchMWchn 83 2116, 1936) itamin A; Richter (ArDuS 179 611 1939), 79 cases, of which etiology was eczema in 23, psoriasis in 12, arsenicals in 12, arsenic in 3, pemphigus in 3, gold in 2, seborrheic dermatitis in 2, mycosis fungoides in 1 pityriasis rubra pilaris in 1 mercury in 1 Hanes and Crew (Endocrinol 21 404, 1939) abnormalities of thyroid function, Zakon and Falkenstein (IllMJ 82 331, 1942) case with marked lymphadenopathy Fraser (ADS 48 42, 1943) leukemoid case Lata (abs YBD 1947 p 286) 27 nonarsenical cases grouped in 4 categories superimposed on preexisting dermatitis, superimposed but persisting after original dermatitis healed, superimposed but eventually entirely healing, and primary without pre-existing dermatosis Rost (ArDuS 187 331 1948) Symmers' disease, prurigo with lymphadenopathy 7 cases, 2 necropsies.

Epidemic Exfoliative Dermatitis (Savill s Disease) was described by Sa ill (BJD 4 35 189 JCutD 1 81 1894) as a peculiar eczematoid affecti n which occurred as an epidem c in several London infirmaries and workhouses during the a t mn months. Smaller outbreaks have occurred since, in the same city a d sporadic cases have been reported by Fo lyce (JCutD 15 141 1897) and Colby and Wi field (JCutD 16: 3, 1898) in this country While the ca se is unknown, the disease perhaps is a syndrome of nutritional deficiency

A observed by Savill, there were two clinical varieties of the disorder: the first was mo t and resembled eczema, th second was dry and simulated pityriasis rubra. The majority of the pat e ts were middle aged or elderly There was generally adenitis involving especially th cervical nodes. The constitutional symptoms were remarkably slight, and there was seldom any precursory o accompanying fever The arms, face and scalp were usuall attacked first The disease began as purplish or reddish macules or papules which t nded to coalesce to form red patches and these in turn spread peripherally until the entire body was i vol ed. The eruption wa , as a rule, symmetrical from the first. Exfoliation commenced early and persisted fo 4 or 5 weeks. The hair and nails were shed in several cases. Some of the early lesions became vesicula at the e d of the second or third day w th the developme t later of moist eczematoid patches. The origin of a few lesion could be traced to local causes, and in th se instances the prompt application of tincture of odine ge erally aborted the attack. The disease usually ran its course in 6 or 8 weeks, but recurrences were frequent. I some of the more debilitated patients death resulted, usually from exhaustion.

The disease was investigated bacteriologically by Savill and by Ru sell (BJD 4: 104, 1892), both of whom isolated a diplococcus in rodlike segm nts, which in some respects resembled the *Staphylococcus* eus, but which did not liquefy gelatin. The histology of the lesions was investigated by Savill and by Echeverria (BJD : 9 189) The former found

engorgement of the vessels, with serous effusion, and extravasation of leukocytes. Echeverria found what he thought to be a remarkable form of degeneration of the prickle-cell muclei. The disorder was little influenced by treatment.

An epidemic follicular eruption was reported by Bowers (ProcRoySocM 45: 459 193_) after there had occurred in Cheltenham some 700 cases of an eruption which appeared suddenly usually without systemic symptoms. In the early stages, a papular erythematous, follicular eruption ppeared, chiefly on the face and back, sometimes on the arms and occasionally on the bdomen. After some 3 or 4 days, horny follicular plugging occurred. The patient were well after 10 days or less, and there were no sequelae. A particular water reservoir seemed to be to blame, for when this reservoi was shut off from the water supply of the community no further cases appeared.

KERATOSIS FOLLICULARIS

The disease was described independently by White (JCutD 7 201 1889) and Darier (AnndeD 10 597 1889)

Darier White s Disease is a rare dermatosis characterized by a symmetric eruption of small, firm papules which are reddish at first but become



Fig. 1191—Keratosis follicularis, typical invol ement of temples, forehead and dorsa of hands. (Dr Bedford Shelmire.)

Fig. 1192—Keratosis follicularis, severe. See Fig. 1197 (Dr W C. Fisher)

darker and enlarge to form papillomatous growths. Lesions occur on the sides of the forehead and neck the nape of the neck over the shoulders and along the midline of the trunk by predilection. When a crust is removed, a minute funnel-shaped depression is left in the top of a papule The lesions are at first discrete but tend to become confluent On the scalp masses of oily crusts are comparable with those occurring in severe seborrheic dermatitis, and alopecia may result (Welton ADS 47 398 1943) As a result of fermentation the lesions may suppurate or ulcerate and emit a highly offensive odor About the genitalia and the anus the lesions may vegetate. The health is little involved, but the victim may be prevented by his disease from earning a living Cases range in severity from mild to extreme.

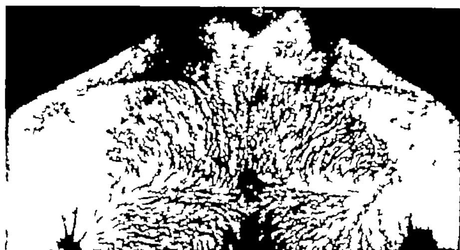


Fig. 1193.—Keratosis follicularis, showing verruca-like lesions scattered about neck. (Dr D. E. H. Cleveland.)





Figs. 1194 and 1195.—Keratosis follicularis. (Dr Gustav Riehl.)

A remarkable case with generalized bullae was reported by Reiss (JID 9: 17 1947) who obtained improvement with vitamin C.

Dyskeratotic lesions were provoked by ultraviolet light and faded when the irritation dissipated in 3 cases of Preissman (AandeD 6: 185 1946). Costello (ADS 65: 494, 1952) too, stressed the ill effect of sunshine. A curious case, affecting the right leg and resembling a linear nevus, made its appearance following severe sunburn reported Robinson (ADS 62: 137 1950). Localized involvement is quite unusual, but Gordon Sauer (in 1955) showed me a man with a patch, histologically proven in a discrete area on one side of the thorax, and Allen (The Skin, Mosby 1954 p. 568) described the rare occurrence of solitary small lesions in the scalp.

Mucosal lesions, even involving the esophagus have been observed (Reenstierna: AfDuS 1 4 841, 1918; Brunauer: Act D-V 6: 131 1925; Frost: ADS 31: 503 1935). The gums were spongy and hypertrophic and the fingernails thin and longitudinally striated in the young woman seen by Harris and White (ADS 59: 346 1949).

Etiology—The cause is not known. Two or more cases may occur in the same family (Hitch et al. SouthMJ 34 578 1941) and inheritance is transmitted through and to both sexes as an irregular dominant character. The relationship to disturbed vitamin A metabolism was recognized by Peck et al (ADS 43: 223 1941) who reported colorimetric studies of blood serum concentrations of A indicating that low values exist in patients on normal diets.



Fig 1196.—Keratosis follicularis of the elbow region in a severe case in old ing a woman with several sibs likewise affected.

Their later studies (ADS 48 17 1943) showed correlations of dark adaptation and low vitamin A values in the serums of 8 of 10 patients. Unless large amounts of A were supplied the serum levels would drop. Carleton and Steven (ADS 48 143 1943) *tested 4 patients and found no evidence of vitamin* A deficiency yet 2 of their patients responded favorably to its administration. No disorder of liver function was detected in 6 cases studied from this point of view by Porter and Brunauer (BJD 61 277 1949).

Pathology—Acanthosis and disruptive loss of cohesion between the basal epidermal layers are typical. In the depths of the lesions are peculiar hyaline, doubly-contoured bodies representative of degenerated epithelial cells (Pels and Goodman ADS 39 438 1939). The dyskeratosis seldom affects a hair follicle though slitlike orifices filled with loose keratinized material are seen at the depths of the interfollicular epidermis and sometimes at the sides of follicles (Ellis: ADS 50 27 1944). Compare familial benign pemphigus. Histologic examination differentiates acanthosis nigricans and other possibly confusing disorders.

Diagnosis.—Keratosis follicularis is to be differentiated from acanthosis nigricans, molluscum contagiosum ichthyosis papillomatosis, and seborrheic keratosis. Acanthosis nigricans commonly attacks adults, the mucous membranes are generally involved early pigmentation is a marked and char

acteristic feature cancerous involvement of some internal organ is almost the rule and Darier's psorosperm like bodies are absent In molluscum contagiosum the eruption is never generalized and the lesions are shiny and pearl-like never greasy and crusted. The history the character and distribution of the lesions, and the absence of follicular involvement will serve to identify ichthyosis. The histologic features of keratosis follicularis are characteristic.

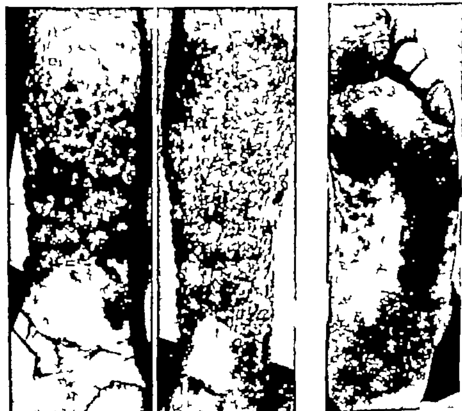


Fig 1197 —Keratosis follicularis, showing extreme involvement of the legs of the patient shown in Fig. 1192. (Dr W C. Fisher)
Fig 1198.—Keratosis follicularis affecting the sole. (Dr J W Perkins)



Fig 1199 —Keratosis follicularis, showing involvement of nails. (Dr J B. Shelmire)

Prognosis —The malady is chronic and usually progressive The symptoms can be ameliorated, but cure cannot be promised. The development of malignancy in the lesions occurs occasionally as reported by Wende (JCutD 26 531 1908) and Charache (ADS 35 480 1937)

Treatment.—Vitamin A in a dose approximating 200 000 units per day is often remarkably helpful Its utilization may be enhanced by giving hydrochloric acid and also perhaps, thyroid. Vitamin A therapy of 100 000 units per day is adequate and should not be abandoned in less than 2 months though it helped not at all in 2 of 7 cases of Porter et al. (ADS 56 306 1947)

found vitamin A ointment without value Improvement followed the ingestion of large amounts of butter but not of vitamin A or margarine, in a case of Levine et al. (ADS 58 564, 1948)





Figs. 1200 and 1201.—Keratosis follicularis Note hydropic change in stratum mucosum, intraepidermal cleft, hyperkeratosis, and "psorosperms." (Dr Fred Weidman.)

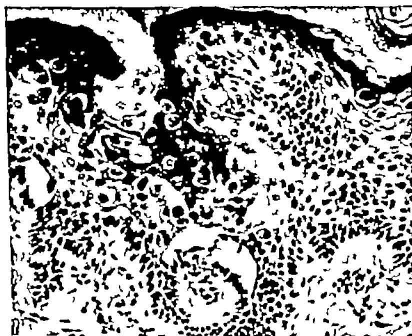


Fig. 1202.—Dyskeratosis of keratosis follicularis. (Dr Hermann Pinkus.)

Locally the generous use of zinc stearate powder is comforting or boric acid poultices, or an ointment containing 1 to 2% of salicylic acid or resorcinol X-ray therapy affords fairly effective palliation, grenz radiation being of

especial value because of the need for inducing epidermal atrophy and the desirability of harming the dermis as little as possible Response to soft radiation is likely to be better than to x rays of shorter wave length (Wise ADS 35 1205 1937 Stoltz DWehn 105 1266 1937) Using grenz ray therapy Weissenbach et al. (BSocfrançD 46 1339 1939) would give a strong erythema dose in 5 treatments, expecting disappearance of lesions, but pigmentation would remain. Hypertonic saline baths, using 2 pounds of rock salt to the tub for 30-minute soaks daily helped a patient of Tye (ADS 66 618 1952) who utilized the idea of Gordon (ADS 52 178 1945) of treating ichthyosis so with palliation. Ointment applications are seldom satisfactory especially in warm weather when the patients are standardly more uncomfortable Spraying secondarily infected skin with chloramphenicol, 200 mg to the ounce of 95% alcohol has helped to tidy up several patients of mine one of whom was well relieved of itching when she took Chlor-Trimeton.

See White (JCutD 9 13, 1891) Bowen (JCutD 14, 29 1896), histology Trimble (J 59 644 1912) 6 cases, soles affected in 4; Bechet (JCutD 37: 332 482, 1919) cases in brothers, Wise and Parkhurst (ADS 2 430 1920) 2 cases, review Gougerot and Burnier (BSocfrançD 40 169 1933) case, vesiculopustular lesions and palatine in ointment Barwasser (ADS 44 941 1941) case responsive to vitamin A Madden (ADS 43 35, 1941) mother and 4 daughters affected, brothers and sons unaffected Beerman (ADS 60 800 1949) vegetative lesions distinguished histologically from nevus syringocystadenomatosus papilliferus.

LUPUS ERYTHEMATOSUS

Lupus erythematosus is an inflammatory dermatosis characterized by the occurrence of pinkish or reddish macular lesions of various sizes and shapes which on subsiding leave whitish, atrophic scars. Lupus erythematosus may be discoid or systemic (disseminated) Cazenave should be accredited with the earliest description of the discoid disease published in 1851 according to Gahan (ADS 66 458, 1952) and the systemic form was first described by Kaposi (AfDuS 4 36 1872)

The discoid form is the more common. It may flare acutely and it is said that there are transitional forms wherein the discoid becomes systemic, a phenomenon I have not witnessed. Scaling and atrophy need not be present and indeed are usually wanting in the systemic diseases, cutaneous lesions of which if present may resemble erysipelas.

The clinical classification of Brocq was followed by Keil (ADS 36 729 1937) who recognized the inadequacy of morphologic classification without consideration of the systemic aspects

(1) Symmetric centrifugal erythema on the cheeks, nose or ears, superficial, pr[illegible]ous, rapidly varying not scaling or scarring an uncommon type which may disseminate This resembles erythema perstans of Kaposi.

(2) The fixed, discoid, scarring lesions of classic lupus erythematosus.

(3) The exanthematous acute or subacute disseminated forms.

There are transitions between the acute and chronic forms. The chronic form may flare with superimposed acuteness.

The grouping which appealed to Michelson (CalifM 70: 8, 1949) divided cases into the chronic which are local or disseminated, and erythematous, edematous, papular (tumid), hypertrophic verrucous or telangiectatic; the subacute, which are local or disseminated and the acute which are disseminated and may be accompanied by high fever low fever or no fever at all

The classification used by Brudick and Ellis (SouthMJ 44 204, 1951) recognized 4 forms chronic discoid; chronic disseminated representative of generalized discoid disease subacute disseminated, or systemic; and acute disseminated, or systemic They judged from biopsy studies of 213 cases that subacute and acute forms may readily be differentiated from the chronic discoid, and that acute cases can be differentiated from subacute and chronic disseminated forms. It is hard, however to distinguish histologically between subacute and chronic systemic forms. In acute cases, the important histologic features are atrophy of the epidermis, edema of its basal layer edema of the upper cutis, and intense superficial cellular infiltration in the upper cutis with the absence of deep inflammatory infiltration. In subacute cases there are less atrophy and edema of the epidermis and less edema but more cellular infiltration of the cutis especially of the deeper parts. In the chronic discoid type, the epidermis is frequently atrophic there is less edema in the epidermis and cutis, and the deep cellular infiltration is fairly characteristic, being arranged in dense well-defined masses.

DISCOID LUPUS ERYTHEMATOSUS

Symptoms.—The lesions are fairly well-defined, macular or slightly elevated dry pinkish or reddish patches They range from the size of a pinhead to that of the palm, and are covered with small grayish, adherent scales. *They develop insidiously Symptoms are slight, described by the patient as* burning or tensive with little itching The affected skin is slightly infiltrated. On the cheeks the lesions are often symmetrically placed. The patches increase in size by both peripheral extension and coalescence. Atrophic changes are characteristic and are conspicuous in patches of long standing In old lesions inflammation is principally marginal the central areas being thin and depigmented with numerous gaping *follicular orifices. Occasionally* the mouths of the follicles are filled with corneous material.

The sites of predilection are particularly the malar eminence bridge of the nose lobe and concha of the ears mastoid area and scalp On the scalp the follicles are involved the patches are sharply defined and cicatricial alopecia is the sequel. Scarring resulted actually in the spontaneous ab-





Fig. 1203.—Discoid lupus erythematosus. (Dr Grover Wende.)
Fig. 1204.—Discoid lupus erythematosus in a Negress (Dr J B. Shelmire.)

sorption of the ear lobes in 2 patients seen by Hollander and Krugh (ADS 62: 142, 1950) The dorsum of the hand is also a likely location, evidently because of exposure to sunshine

Hasselmann (ADS 29 585 1934) reported cases from the Philippine Islands. Half as frequent in the Negro as in the white (Cummer ADS 33 434 1936) the disease sometimes produces in the Negro hypertrophic scarring with bizarre depigmented, keloidal lesions.

Mucous Membranes are involved in about 25% of the cases (Smith BJD 18 59 1906) *The lesions may consist only of slight thickening with duskiness and scaliness,* or some abrasion may be present. The mucous surfaces most commonly attacked are those of the lips (Folpmers DZtschr 75 326, 1937) eyelids cheeks and tongue. Healing is accompanied by atrophic thinning and partial loss of color Subjective symptoms are nearly always absent. Conjunctivitis, described by Klauder and DeLong (AOphth 7 856 1932) Montgomery (ADS 37: 417 1938) and others, is characterized by velvety edema with extreme redness, which may come and go rather rapidly or may persist like the discoid skin lesions usually accompanying it.

Similarity between lupus erythematosus and the Hunner ulcer of the bladder was remarked by Fister (JUrol 40 37 1938) Interstitial cystitis, like the skin disease tends to spread peripherally and results in atrophic scarring

INVOLVEMENT OF INFANTS.—The occurrence of the disease in infancy and childhood rare has been described by Cummer (ADS 24 999 1931) It may begin in the first year of life. In his series, the ratio of females to males was 7 3





Fig 1205—Discoid lupus erythematosus (Dr A. L. Anderson)
Fig 1206—Discoid lupus erythematosus in a Cherokee Indian (Dr Everett S Lain)





Fig 1207—Discoid lupus erythematosus somewhat warty (Dr W Herbert Brown)
Fig 1208—Discoid lupus erythematosus involvement of lip is not rare

FAMILIAL INCIDENCE is probably coincidental but cases affecting 3 sisters were reported by Jaworowska (UCutRev 48 333 1944) and affliction of a brother and sister by Zeisler and Bluefarb (ADS 49 111 1944)

Deep hypertrophic discoid lupus erythematosus is a recognizable variant in which the lesions are more or less vegetative, with deep pits and depigmentation (Bechet ADS 45 33 1942 61 495 1950) Papular and nodular forms are also seen (Fordyce JCutD 36 585 1918; Irgang ADS 43; 281 1941) The firm sharply outlined, movable, subcutaneous tumors of lupus erythematosus profundus were said by Arnold (ADS 57: 196 1948) to resemble sarcoid clinically but to consist histologically of compact periglandular

and perivascular lymphocytic infiltrations. Arnold's case not hypersensitive to tuberculin or responsive to bismuth was cured by intravenous gold. A case of tumorlike form was noted by Irgang (ADS 48 60 1943) and profundus cases have been noted by Mitchell Heggs (BJD 62 503 1950) and Costa and





Figs. 1309 and 1310.—Discoid lupus erythematosus. (Dr Gustav Riehl.)





Fig. 1311.—Atrophic scarring and depigmentation are expected in discoid lupus erythematosus.

Fig. 1312.—Atrophic scarring and depigmentation. (Dr J P Gusquierra.)

Junqueira (AnndeD 82 144 1955) Pautrier (AnndeD 80 233 1953) said he never saw such a case, believed that Kaposi and Brocq had not, and evidently doubted that anyone ever had or would. Irgang (AnndeD 81 246, 1954) disagreed with him. Arnold (TransactAD \ Apr., 1955) reviewed the

subject and reported 4 cases, distinguishing from Bechet's the cases wherein the epidermis is much affected for the profundus type is subcutaneous, although subcutaneous lesions in the systemic disease may simulate them.

LYMPHOCYTIC INFILTRATION OF THE SKIN, a condition resembling deep discoid lupus erythematosus, was identified by Jessner and Kanof (ADS 68: 447 1953) in their presentation of * cases. Jessner summarized the clinical picture, course, diagnosis and histology as follows: The lesions are flat, discoid, more or less elevated, pinkish to reddish brown starting as small papules, expanding peripherally sometimes clearing in the center sometimes showing a circinate arrangement. The surface is smooth, occasionally uneven. There is no follicular hyperkeratosis. The consistency is firm. There may be only one, a few or numerous lesions. They persist for weeks or months or longer disappear without sequelae, and may recur in the same or other areas and cause practically no subjective symptoms. The face is the area of predilection, but othe parts of the body may or may not be affected. These cases must be distinguished particularly from cases of chronic



FIG. 1211.—Cicatricial alopecia of the scalp, due to discoid lupus erythematosus

discoid l pus erythematosus, under which label they are invariably described; also from sarcoid, tuberoserpiginous syphilid, and drug eruptions. There are o enlarged lymph nodes. The blood cell count shows only an occasional relative lymphocytosis. The bone marrow smear reveals no abnormalities.

Histologically the findings are rather constant. The epidermis may be stretched but is otherwise uninvolved. There may be edema in the subpapillary region in fresh lesions older ones show none. Distributed through the cutis are rather sharpl circumscribed, lymphocytic infiltrations, sometimes extending to the subcutaneous fat, frequently but not always, around vessels and/o appendages. The infiltrates consist of lymphocytes mostly small ones and usually a few histiocytes and plasma cells. The infiltrates are often enmeshed in a fine reticulum. There are no eosinophils, no germinal centers or germinal center like formations.

They separated this disorder also from true lymphocytoma, the reticuloses, the lymphoblastomas and the Spiegler Fendt sarcoid. Kimmelman (ADS 68: 445, 1953) stated he had seen 5 c ses with Rein, and that those treated with Atabrine had been cured.

Telangiectatic discoid l pus erythematosus—The t langiectatic form is rare (Bechet ADS 58: 128, 1948 see Heimburger: CinMJ 38: 563 19*4) Originally described

by Crocker (Diseases of the Skin, Blakiston, 1888) it may be representative of benign lupus erythematosus or in the form of erysipelas perstans faciei (Kaposi: AfDuS 4: 36, 1872) it may occur in the systemic disease (Robertson and Klauder: ADS 8: 487 1923)

Figs. 1214 and 1215.—The left cheek of this man shows advanced squamous carcinoma developing in the scars of discoid lupus erythematosus the right cheek shows marked scarring.





Fig. 1216.—Classic discoid lupus erythematosus

Fig. 1217.—Atrophic lesions of discoid lupus erythematosus with squamous carcinoma of the lip in the lupus scar: the man was 25 years old.

A a subvariety of discoid l pus erythematosus the telangiectatic disease is characterized by points, spots, plaques, or large disks on the surface chiefly of the face usually well defined ad of rosy-reddish or deep purple colo which deepens under pressure The olor is due to dilat tion of the cutaneous vessels. The surface may be either slightly edematous or infiltrated and correspondi gly elevated. Absent re scaling and dilated

follicles, but typical scars not infrequently follow involution. The course of the disease in this form is slow and the condition may remain for years without change. (Ormsby and Montgomery. Diseases of the Skin. Lea & Febiger 1948, p. 947.)

Etiology.—The cause is unknown. Circulatory disturbances and actinic trauma are predisposing factors. Sunshine is extremely harmful. The majority of the cases occur in women. The incidence, sites of predilection, geographic distribution of cases and other etiologic aspects were studied by Gahan (ADS 45 685 1133 1942) whose statistics are interesting though not revealing. The hypothesis of vasculoallergic response to microorganisms appealed to Stokes et al. (AmJMedSci 207 540 1944). Focal infection was generally present in the cases of Cerri (abs YBD 1939 p 168). His experience parallels my own with respect to the generally beneficial effects of eliminating foci.

Attempts to prove the disorder tuberculous or paratuberculous have been unsuccessful. The fact that it is extremely rare in sanatoriums for tuberculosis (Markley pers comm. 1953) is in favor of its nontuberculous nature.



Fig. 1218.—Lupus erythematosus, involving the tongue. (Dr George Miller MacKee.)

Roth (AfDuS 51: 2, 247 396, 1900) found evidence of tuberculosis i 70% of a series of 250 cases which he investigated, Boeck in about 60% and Fordyce and Holder in several instances. I agree with Weiss and Singer (AmJMedSci 155 5-6 1918) that no evidence has been presented as yet that shows a direct relationship between this type of lupus erythematosus and tuberculous infection or tuberculous disease. Keil (ADS 28 65 1933) felt that the occurrence of tuberculosis in lupus erythematosus is coincidental only. Wise and Sulzberger (YBD 1934, p. 355) inclined toward the belief that several causes may equally provoke the disease, and that in Europe tuberculosis is the commonest. Kren (Del 9CongrInternatDermat IX 2: 701 1935) reported finding tuberculosis in all of 94 cases and averred that the proportion of lupus erythematosus cases yielding tubercle bacteria on culture is higher than in any other form of cutaneous tuberculosis. Gray (BJD 37 406 1925) after summing up the evidence concluded that lupus erythematosus is a definite clinical entity that it is a specific, infective disease that the lesions are due to the local activity of a specific microorganism; that there is not sufficient evidence that this organism is the tubercle bacillus; that tuberculosis is a common accompaniment of the disease and that streptococcic infection is a fairly frequent terminal manifestation, especially in the acute types. Skin tuberculosis differs from lupus erythematosus in the dense and world distribution (Gahan: ADS 46 131 1942).

Pathology.—Early changes consist in dilation of the superficial vessels, followed by extravasation first of leukocytes, then of lymphocytes and monocytes (Montgomery JID 2 343 1939). Epidermal changes, probably sec-

ondary to dermal inflammation, are of diagnostic value comprising irregular hyperkeratosis, keratotic plugging of follicles and ducts, preservation of the granular layer acanthosis side by side with atrophy of the prickle cell layer and liquefaction necrosis of the basal layer Infiltration is chiefly lymphocytic and is located about the vessels and appendages. The cutis is edematous, and elastic tissue is damaged in infiltrated regions. Walls of deeper blood vessels do not show proliferative or obliterative change. Atrophic scarring characterizes the late stages. Histologic distinction of discoid from systemic lupus erythematosus on the basis of skin lesions seemed impossible to McCreight and Montgomery (ADS 61 1 1950) the same changes being found in all the lesions though with some variation as to degree. This variation appeared to depend more on the stage of evolution of the individual lesion than on the type of case from which it had been removed for study

Diagnosis.—The well-defined type of lesions, their history course shape color consistency and distribution, together with the presence of atrophy should prevent error



Fig. 1310—Lupus erythematosus Discoid lesion, typical histologic structure. Note relati and absolute hyperkeratosis; keratotic plugging of hai follicle and sweat duct; alternat trophy and acanthosis of the epidermis; areas of liquefaction necrosis of basal cell layer; merging of connective and lastic tissue to form collacin in papillary body; and dense perivascular lymphocytic infiltrate. (Dr Hamilton Montgomery)

Contact dermatitis, psoriasis, seborrheic dermatitis, superficial epithelioma, lupus vulgaris and syphilis are to be excluded. Eczematous lesions are itchy not sharply margi ated, often vesicular and do not sc r. In psoriasis, scale formation is prominent, and bleeding points can be demonstrated. Seborrheic dermatitis is seldom sharply defined, and scarring is never present. Lupus vulgaris generally begins in childhood; the scars are seldom soft and atrophic but are usually rough, corded and conspicuous; typical, pple-butter-colored nodules occur t the margins of a tuberculous lesion. Tubercular syphilids commonly give rise to more or less scarring, but the cicatrices are smooth and marked by patulous gland rifices. The lesions develop rapidly individual nodules are usuall present, th re is a tendency to ulcerate, nd the blood test is positive. Epith lioma has a definitely sh rp margin when closely scrutinized.

Prognosis.—Discoid lupus erythematosus is chronic disease capricious and erratic in its course with relapses and occasional recurrences likely to occur Occasionally the lesions disappea sponta eously Sometimes new patches develop and older ones extend despite the use of approved therapeutic measures. Onset at age 20 months occurred in the case of Becker (ADS 50: 424 1944) in the discussion of which Ormsby said the prognosis in the young child is favorable. Dissemination is possible and is ominous when it occurs. Approved therapy itself entails dangers; see dermatitis medicamentosa, gold, Atabrine.

On the scars of old discoid lupus erythematosus occasionally develops squamous carcinoma, as in cases of Dicke (DWehn 44: 24, 1925) Ryan (BMJ 2: 334 1947) Wolstenholme (BJD 61: 126, 1949) and Snapp (ADS 62: 166 1950); see carcinoma etiology scar Determination of the sedimentation rate appeared to have some prognostic import i the series of 83 cases studied by Cochrane (ADS 63: 323, 1951)

Treatment.—Eradication of foci of infection is strongly to be advised. The benefits have been conspicuous in many cases in my experience see Hartzell (ADS 2 44 1920) Foreign protein therapy is hazardous. The patient should perhaps be advised to limit coffee tea chocolate cream and alcohol. The avoidance of sunshine is a necessity

In choosing a local agent it is wise to begin with mild, soothing lotions. As good as any is calamine lotion with 0.5% of phenol. Patches may be cleansed by means of mineral oil and can be protected from sunshine with a sun screening ointment such as Afil. Remedies such as 10% Ichthyol in collodion or in ointments, or weekly applications of pure phenol or of a saturated aqueous solution of lactic acid may be tried. Hollander s combined method sometimes proves helpful the patient is given quinine sulfate 0.5 Gm t.i.d. daily for from 5 to 7 days each evening the lesions are painted with tincture of iodine at the end of the period the treatment is discontinued until the crusts have become detached. Then if necessary another course of treatment is instituted.

Solid carbon dioxide is excellent in chronic discoid cases. One application under moderate pressure for 2 seconds may suffice

A paste such as one might prescribe for tinea containing 4% sulfur 3% salicylic acid and 6% benzoic acid, applied lightly once a day is sometimes remarkably helpful

Roentgen, radium and ultraviolet radiation are worthless or *harmful*.

When the lesion of 10 years duration was replaced by full thickness skin graft in the case of Quiqoba (abs BJD 59: 317 1947) lupus erythematosus recurred within the graft 7 months later A similar experience was reported by Flynn (AustralJDermat 1 194 1952)

Atabrine (quinacrine Mepacrine) was introduced in the treatment of lupus erythematosus by Page (Lancet 2 755 1951) who reported excellent results in 8 of 18 cases, good in 5 little in 3 and some in 1 case of the systemic sort. Various dosage schedules were *tried, but 100 mg 2 or 3 times* a day was satisfactory The degree of improvement appeared to be related to the development of yellow staining of the skin.

The drug was first recommended by Prokoptchouk (abs ZentralblHuG 66 11, 1940 1941 see AD 71 520, 1955) but, while its use became standard in the U.S.S.R., the report was overlooked outside the Iron Curtain. Confirmation of the good effect and little danger of the chemical was made by Cramer and Lewis (JID 19: 293, 1952) whose 6 patients rapidly improved; by Sawicky et al. (JID 19: 397 195-) with 6 cases, 1 ... with good results in 9 cases improved and 3 unresponsive; by Wells (JID 19: 405 1952) with good results (BJD 65: 196, 1953) who of 1 by Sommerville et al. (BJD 64 417 1952); by Black (BJD 65: 196, 1953), ga e concomitantly para aminobenzoic acid by Courville and Perry (ADS 67: 510 1953), in 13 cases, ot all of which underwent complete remission; and by O'Leary et al. (ADS 67 633, 1953) The ill effects are those of drug intolerance, and one must be alert to toxication (Harvey and Cochrane JID 21 99 1953) The production of yellow pigmentation and increased tolerance of actinic light i not necessary for obtaining beneficial ffects, for the M.E.D of U.V light in patients under treatment wa sometimes low while the drug wa being given with improvement and high when it was withdra n and the patie t howed relapse (Bettley and Page: BJD 66: 237 1954)

Intradermal i jections of quinacrine locally were combined with it oral administration by Ottolenghi Lodigiani (abs J 157: 1584 1955) who claimed advantages in the results as compared with oral treatment alone

See Dermat t medicamentosa, quinacrine; Lichen planus, qui acrine (p. 909)

The dose may be 0 1 Gm t.i.d. or smaller until pigmentation is fairly conspicuous then 0 1 Gm daily Not all cases respond and, of those that do, some relapse when the drug is withdrawn. The pigmentation is objectionable but in general is preferred by the patient to active discoid lupus erythematosus. If benefit does not take place within a month, it is unlikely to take

place at all (Kierland et al. ADS 68: 651 1953) A high proportion of the cases are helped, but not all of them, according to Cole et al. (J 153 1515 1953) who found that those who did clear completely stayed clear.

Chloroquin, being not productive of discoloration of the skin was tried in a dose of 0.25 Gm. twice a day for a week or two followed by 0.25 Gm. daily for from 4 to 6 weeks, and appeared to yield effects as good as those of Atabrine reported Goldman et al. (J 152 1428 1953) Its effectiveness has been attested also by Pillsbury and Jacobson (J 154: 1330 1954) Harvey and Cochrane (JID 22 89 1954) and Rogers and Finn (ADS 70 61 1954) One may not be casual about the dosage, for the drug is excreted slowly. The usual toxic symptoms are nervous restlessness confusion insomnia, even hypomania. Chloroquin is capable of causing pruritus, nausea, diarrhea, headache visual difficulties, loss of weight and lichenoid dermatitis.

Bismuth given intramuscularly has been highly recommended (MacKenna Lancet 1 178 1930) Tolman (NEngJM 219 688 1938) judged from his review of 122 cases that bismuth is as effective as gold being safer it should be tried first (Smith BJD 46 399 1934)

Gold sodium thiosulfate is given intravenously. It should not be used indiscriminately. The agent is a valuable one (Martenstein KlinWehn 1 2235 1922 Schamberg and Wright: ADS 15 119 1927 Wright ADS 33 413 1936 Bechet NYSJM 42 609 1942) Yet of 31 patients treated with gold 74% relapsed (Callaway and Stokes ADS 37 627 1938) An initial dose of 5 milligrams of gold sodium thiosulfate is probably safe. Subcutaneous administration is as effective as intravenous (Jones and Alden ADS 28 544 1933 J 107: 1203 1936) Weiss et al. (ADS 35 1074 1937) found that the discoid cases as well as the disseminated ones tend to have leukopenia. When giving gold, the white blood cell count should be followed with care and caution. A patient may respond to doses of 50 to 100 mg. if unresponsive to 10 mg., said Wise (ADS 40 668 1939) but the hazard of thrombocytopenia must continually be borne in mind.

Gold was not found spectroscopically in active lesions of patients under gold therapy but it was present in the healed scars of patients so treated (Beinhauer et al.: ADS 50 315, 1944) Bismarsen was the choice of Weiss et al. (ADS 44: 1009 1941) who admitted the necessity of constant observation of cases so treated.

Gold sodium thiosulfate 0.06 cc. of the 1% solution with procaine, may be injected at each of several sites about the periphery of the lesions without complication, curing some patients in whom intravenous gold has failed, according to Monash and Traub (ADS 50: 318, 1944)

Mapharsen, recommended by Sulzberger helped a patient of Baer (ADS 49: 131, 1944) and several patients of Hyman (ADS 53 26 1946) Goldberg (ADS 52: 89 1945) gave 0.02 Gm. Mapharsen intravenously twice a week to 21 patients, who, he said, promptly improved.

Suramin (Germanin) the hazards of which are emphasized, was spectacularly helpful in a case of Costello (ADS 54: 736 1946) and was beneficial after other drugs had been tried in a case of Yontef (abs YBD 1949 p. 65) to whom it seemed to be less dangerous than it does to me.

The administration of sulfonamide, in a dose seldom exceeding 0.5 Gm. 3 times a day, was recommended by Barber (Lancet 1: 583, 1940; BJD 53: 1 34, 1941) who also advised elimination of focal infection. A febrile reaction and malaise for 8 to 14 days were expected, he said and a generalized scarlatiniform eruption, Herxheimer-like was not to be considered alarming although during such a reaction the drug should be stopped. He thought this treatment beneficial when the case depended on streptococci infection but without value when the cause was tuberculous. Glyn-Hughes and Spence (BMJ 741 1940) confirmed his findings while they acknowledged the hazards.

Vitamin E yielded good improvement and a lessening of photosensitivity in patients given from 100 to 300 mg tocopherol daily reported Burgess and Pritchard (ADS 57: 953, 1948)

Vitamin B_{12} in large doses was recommended by Goldblatt (JID 17: 303 1951) This harmless treatment was approved by Marcus et al. (JID 21: 75, 1953) who assessed it as inferior however to gold or bismuth.

Isoniazid in a dose gradually increased from 1 mg./kg. daily to as much as 4 mg./kg diminishing if gastric distress appeared, was given in 3 cases by Eddleson (JID 1: 1, 1953) with evident benefit. Its effects while beneficial, were deemed unspecific by Appel et al. (ADS 68: 417 1953)

Rutin in a dose of 1.0 Gm. given several times a day was said to have cured 10 of 32 cases, while 11 got worse (Serowy DWehn 127: 590 1953)

Cortisone is unreliable but sometimes, in a dose of 25 mg. daily stops the spread of the disease. Its use is dangerous if tuberculosis is present. Topically it appeared helpful in some cases of Newman and Feldman (JID 17: 3 1951) more might be expected of hydrocortisone ointment, although its effects are not remarkable here Interestingly Pusey and Rattner (ADS 31 865 1935) obtained benefit with desiccated adrenal substance.

See Goeckerman and Montgomery (ADS 25: 304 1932) pathology; MacCormac (ProcRoySocM 28 107, 1934) acetarsone therapy, Lomholt (DWchn 101: 817 1935) chaulmoogra oil therapy Golshmid (ActaD-V 17: 33 1936) $KMnO_4$ 1.0, H_2O 10 cc, stand 24 hours, add C_2H_5OH 10 cc., with resultant brown paste swab lesions daily; Hopkins and Burky (ADS 33 1060, 1936) intradermal staphylococcus toxin causes in L. E. abnormally vigorous reaction Callaway (ADS 35: 1138 1937), chaulmoogra oil ineffectual Barber (BMJ 2 771, 1937), Prontosil helpful Ingels (ADS 37 879 1938) sulfanilamide beneficial Obermayer and Becker (JID 1: 85, 1938), gold therapy using ammonium succinimide aurate; Pautrier et al. (BSocfrancD 46 966 ff 1939), etiology unknown; Kirby Smith (FlaMAJ 26: 111, 1939) in Negro boys, Kierland et al. (PSMMC 15 676, 1940) review Yousefova and Bogdanovitch (abs ADS 41 388, 1940) conjunctival, Arutiunov et al. (ADS 44: 1116, 1941) thymol therapy; Hall (ADS 47 610 1943) in red part only of forearm tattoo Pfeisky (ADS 54: 33, 1946) psychosomatic aspects; Schmidt (ADS 56, 246, 1947), colloidal gold sulfide plus nicotinic acid vasodilation Zarafonetis et al. (JID 11 339 1948) para-aminobenzoate therapy Anderson and Musgrave (ADS 59: 247, 1949) conjunctival, Robinson (JID 14 309, 1950 ADS 64: 665, 1951) chloramphenicol beneficial Grund (ADS 61: 79, 1950), unusual case, discoid and subcutaneous lesions, cured by PABA Huff et al. (JID 14: 21, 1950) plethysmograph studies of peripheral blood flow in discoid L. E. suggesting systemic vascular disease, Rice (J 155 1601, 1954) chemistry of chloroquin and quinacrine Buchanan et al. (SouthMJ 47: 678, 1954) Atabrine effective in from 60 to 90% Kennedy et al. (JLaMS 106 89 1954) Atabrine benefits Rhodes and Allende (CalifM 80: 78, 1954) Atabrine failed in 4 of 25 cases, Lewis (BMJ 1: 329 1955) chloroquin effectively palliative, but not always; Stoughton (IIMJ 107 290 1955) chloroquin preferred to Atabrine.

SYSTEMIC (DISSEMINATED) LUPUS ERYTHEMATOSUS

Symptoms.—The disease occurs in two clinical types (1) the gradually disseminating with lesions which resemble the discoid, after which the disease may either subside or by a long debilitating course lead to death; and (2) acutely disseminating with flares in which cutaneous lesions resemble erysipelas or erythema multiforme and with visceral involvement productive of fever prostration and the likelihood of death within a few months. Cutaneous lesions range from 1 to 10 cm. in diameter and are usually superficial, dry and red in color Occasionally they are infiltrated or bullous in character resembling eruptions occurring in some cases of dermatomyositis. The regions commonly involved are the face V of the neck and dorsa of hands and forearms, but no part of the body is exempt. Mucous membranes are often attacked. Lesions may come in crops, some patches persisting indefinitely and others disappearing spontaneously with little scarring only to be replaced from time to time by new patches.

The patient is ill and loses weight. The course is erratic with unpredictable remissions. Fever is of bad omen. Leukopenia or leukocytosis may occur The disease is diagnosticable in the absence of skin lesions, being a systemic disorder of unknown cause with variable pathologic picture and a variable symptomatology (Reifenstein NYSJM 42 2227 1942)

Clinical manifestations of the disease are often incited by excessive exposure to sunshine as in the case of Michelson (MinnM 22 565 1939) a woman of 31 who after a test dose of ultraviolet light, developed a generalized eruption and eventually died Initial symptoms may be arthritis, fever pleurisy or lymphadenopathy (Hertzman and Munroe CanadMAJ 59: 416, 1948)

Visceral Lesions noted by Rose and Goldberg (MedClinNoAm 19 333, 1935) attributed by them to widespread vascular damage produced symptoms including fever of septic type weight loss, weakness, bone and joint pains, abdominal pain, headache cough, dyspnea hemoptysis, nephritis, albuminuria, verrucous endocarditis disseminated telangiectases, hemorrhagic or fatty hepatitis terminal bronchopneumonia pulmonic abscess, tuberculous or nonspecific lymphadenitis focal and metastatic infection and retinitis, all of which were observed, though not in one patient. Rose and Goldberg's experience conformed with that of many others in revealing that *it is dangerous to attack foci of infection* although they are usually present transfusion like-



Fig. 1219.—Acute systemic lupus erythematosus typical rash of facial distribution, in a young woman. (Dr J P Guequierre.)

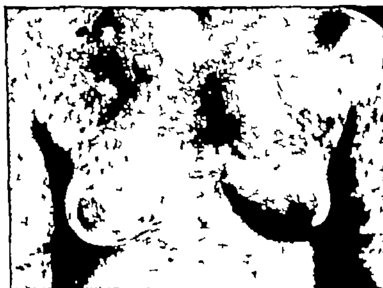


Fig 1221.—Lupus erythematosus, acute The rash centers about the V of the neck. (Dr Max Jessner from Wiener Skin Manifestations of Internal Disorders Mosby 1947)

wise failed to benefit. These cases of disseminated lupus erythematosus presented, typically prolonged fever mucosal involvement, depression of the bone marrow sensitivity to sunshine and preference for females (22 of 23) Jarcho (BullJHH 59 262 1936) confirmed such findings and called attention to the retinal damage which sometimes accompanies the disease In a boy under my care in 1938 there were repeated episodes of fever lowering of blood pressure asthenia, leukopenia and constipation the last being presumably due to loss of smooth muscle tone When this patient stopped losing weight, his course toward recovery seemed established yet he eventually died. No hint was obtainable as to why the exacerbations took place. Leukopenia is not an invariable finding and in milder cases or milder stages of a case leukocytosis of 10 000 to 15 000 may be found Blood cultures are sterile.

VARIOUS MANIFESTATIONS.—The features of a case may emphasize any combination of the following: pleuritis, pleural effusion pericarditis, pericardial eff sion peritonitis, perisplenitis, pneumonia, nephritis, nephrosis, hyperplasia of bone marrow lymphoid hyperpla ia, myocarditis, valvulitis and miscellaneous vascular lesions, Laipply and Longley (ClinBullWestResUniv 4: 31 1940) observed. Hollander et al. (ADS 25: 253, 1932) reported a subacute case with a blood picture resembli g aleukemic leukemia and thrombocytopenia. The case of Templeton (ADS 29: 00, 1934) was also thrombocytopenic. While most patients are female, the 17 year-old boy of Gl gler and Fox (AIntM 65 26, 1940) suffered polyarthralgia especially and died with pericarditis, leukopenia, and renal damage following the removal of a focus of infection. Periarterial fibrosis of the spleen occurred in 15 of 18 cases of Kaiser (B BJHH 1: 31 1943) Thromboc topenic purpura was the conspicuous feature in the case of Eversole (BullJHH 96: 10 1935)

Lymph nodes are enlarged locally or generally in about two-thirds of the cases (Fox and Rosahn AmJPath 19 73, 1943) The nodes i vol ed, in order of frequency are the cervical, mesenteric, axillary inguinal and retroperitoneal. Histologically they show nonspecific changes of edema and engorgement an l perhaps, area of necrosis.

Neurologic symptoms are occasionally the presenting symptoms of the disease (Sedgwick and VonHagen: abs J 139: 833, 1949) and are explicable on the basis of focal vascular lesions or indirectly by reason of renal damage Toxic psychosis, neuroutis, focal vascular lesions chorea and hemorrhages have been noted. Epilepsy actually preceded other clinical evidences of the disease in cases also showing arthritic and leukopenic changes, reported Russell et al. (AIntM 88 8 1951) Not only focal but also disseminated encephalomalacia was found in autopsy material by Glaser (ANeurPsych 67: 43 193) attributable to primary disseminated endarteritis of the smaller vessels. Spinal cord i farction paralyzed the lower extremities in the case of *Piper* (*J 153: 214 1953*)

Etiology and Pathology— A diffuse disease of the peripheral circulation usually associated with lupus erythematosus and endocarditis was studied by Baehr et al (AmJPath 11 881 1935) with 23 necropsies. The basic pathologic change seemed to be a necrotizing injury of the small vessels, with thrombosis and hemorrhage 13 of the 23 patients had verrucose endocarditis glomerular capillaries were occluded, forming hyaline cords described as wire loop lesions, the finding of which was confirmed by Rose and Pillsbury (AnnIntM 12 951 1939)

Cardiac lesions of the atypical verrucous sort characterizing the Libman Sacks syndrome existed in 4 of the 23 fatal cases studied by Gross (AmJPath 16 375 1940) Verrucous, anuclear thrombi which are sterile and which resemble the lesions noted by Baehr were produced in the hearts of rabbits by Andrei and Revenna (AIntM 62 373 1938) who injected intraperitoneally normal rabbit blood horse serum milk and other substances and observed the development of a peculiar form of thromboendocarditis. A small amount of an endocardial vegetation served on injection to transfer the disease which they therefore judged to be perhaps of virus nature the sterile injections having presumably aroused a latent infection

The visceral lesions are dependent upon hyaline thrombi and minute infarctions in the kidneys heart and lungs and in the skin also according to *Kell (ADS 36 729 1937 BJD 49 221 1937)* The skin and visceral lesions have a common cause and either may exceed the other in severity The Libman-Sacks syndrome is manifested by verrucose endocarditis with bacteria-free vegetations and the eruption of systemic lupus erythematosus, while Aschoff bodies are lacking (Belote and Ratner ADS 33 642, 1936) This is





Fig. 1232.—Subacute disseminated lupus erythematosus. The patient recovered.

Fig. 1233.—Acute systemic lupus erythematosus, fatal. Depigmentation was produced by the otherwise inconspicuous cutaneous lesions (Dr O G. Costa.)





Fig. 1234.—Acutely disseminated discoid lupus erythematosus, exacerbation having followed gold therapy and exposure to sunlight. Forehead was protected from light by hat. (Urbach BJD 51 342, 1939.)

Fig. 1235.—Face of boy shown in Fig. 1233. (Dr O G. Costa.)

in fact *lupus* erythematosus Keil believed, for the original description precluded this diagnosis only on the *specious* argument that the absence of atrophy is incompatible.

Renal changes terminating in uremia were reviewed by Stickney and Keith (AIntM 66 643 1940) *who noted* resemblances only not identity with glomerulonephritis. The urinary *findings* are remarkable in that every thing ' may be found red blood cells, all kinds of casts, and protein, a diagnostic heterogeneity (Krupp AIntM 71 54 1943) Adrenal insufficiency (Jager ADS 46 362, 1942) and retinal damage (Maumenee AmJOphth 23 971 1940) are among the features that have prompted publications of cases. An electrocardiogram may *enable* one to detect small necrotic foci in the myocardium (Humphreys AnnIntM 28 12, 1948)

Pulmonary lesions including *pneumonic* processes and pleural effusions were demonstrated in some patients roentgenographically by Israel (AmJMed Sci 226 387 1953)

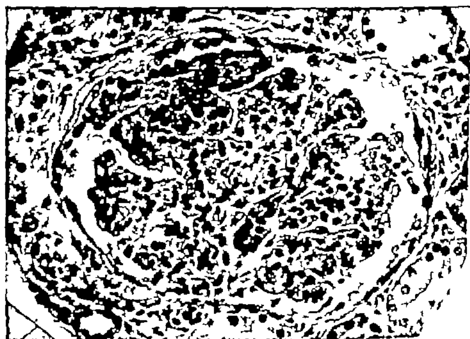


Fig. 1324.—"Wire loop" lesion of kidney glomerulus, from a fatal case of systemic lupus erythematosus (*Rose and Pillsbury* AnnIntM 12 951 1939)

Lane (SouthMJ 31 587 1938) advanced reasons for believing that dermatomyositis is in reality a form of erythematous lupus. Muscle biopsies were compared with those from dermatomyositis by Madden (ADS 62 192, 1950) who found nodular myositis in some cases of lupus erythematosus but no degenerative processes unless lupus was accompanied by rheumatoid fever arthralgia or arthritis. He felt that muscle biopsy is of little differential diagnostic value but he did not find L.E. cells in patients with dermatomyositis. His patients with lupus who did not have L.E. cells were the ones which died, so that their presence seemed to him to be of good prognostic omen. The various organic changes have in common a pathologic involvement of collagenous tissues such as may be induced by *repeated* intravenous injections of foreign protein, according to Klemperer et al. (APath 32 569 1941; J 119 331 1942, NYSJM 4. 2223, 194.; J 114 1109, 194 ; AnnIntM 28 1, 1948) representative of colloid imbalance with variable degrees of disturbed function not necessarily related to allergy

After reviewing 154 cases seen until 1938 plus 132 more seen through 1947 Montgomery and McCreight (ADS 60 356 1949) concluded that the diagnosis of systemic lupus erythematosus may be made in the absence of cutaneous lesions. Acuteness of the disease is accompanied by higher sedimentation rates, more reversals of the A/G ratio and a greater incidence of false positive STS. The systemic nature of the disease they accepted, but it did not appear to be a collagenous disease nor was there evidence supporting an endocrine or allergic origin. They found alterations of collagen and vessel changes in less than 5% of the cases.

There were high sedimentation rates and marked increases in serum gamma globulin in patients of Coburn and Moore (BullJHH 73: 196, 1943) and some showed a false positive Wassermann test (see White: AmJSyph 31: 235, 1947) False positive STS may antecede early symptoms of systemic lupus erythematosus and so deserve serious consideration as possibly foreboding this probably eventually fatal disease, according to Haserick and Long (AnnIntM 37: 559 1952)

Hematoporphyrinuria was found in some cases by Lady and Corson (ADS: 37: 403, 1938) and they also detected lead in the urine by spectroscopy

Heparin when given intravenously did not increase the clotting time in systemic lupus as much as it did in control patients; its action seemed somehow to be vitiated, reported Borris (BJD 63: 21 1951)

The hypothesis that the disease is d e to streptococci was propounded a d investigated by Welsh (JID 10 306, 1948)

Drug sensitivity can cause symptoms resembling if not identical with, systemic lupus. L.E. cells were demonstrated in 3 patients with severe dermatitis medicamentosa from penicillin, hydantoin and Pyramidon by Miescher and Delacretaz (SchweizMWchn 83: 536 1953) who noted that a fourth of Haserick s cases gave the history of epilepsy and may have been hydantoin-sensitive patients. Various other drugs including sulfonamides have ind ced the same phenomenon (Myler: abs J 156: 86 1954) Apresoline (Hydralazine) hydrochloride, when given for a long time in treating high blood pressure has been known to cause syndromes simulating systemic lupus erythematosus, including in one case a positive L.E. cell phenomenon (Perry an l Schroeder: J 154: 670, 1954) Similar cases have been reported by Reinhardt and Waldron (J 155: 1491 1954) and Shackman et al. (J 155: 1492, 1954)

When washed, group O Rh positive erythrocytes are mixed in a saline solution of egg albumin with plasma from a patient with acute lupus at refrigerator temperature, aggregation of the red blood cells occurs (Schleicher: Sci 113: 583 1951) Confirming this observ tion Seale and Mathieson (Sci 115: 528, 1952) thought the phenomenon similar to or identical with the phenomenon of cold agglutination frequently found in patients with primary atypical pneumonia and other illnesses.

The activity of compleme t was subnormal in 12 of 27 patients whose serums were studied by quantit tive spectrophotometry by Elliott and Mathieson (ADS 68: 119 1953) There was some correlation between activity of complement and serum albumin figures, sedimentation rat leukocyte count, demonstrability of L.E. cells, skin lesions and fever

L.E. Cell Phenomenon —A phagocytic phenomenon in patients suffering from acute disseminated lupus erythematosus was observed in bone marrow preparations by Hargraves in 1946 Hargraves et al. (PSMMC 23 25 1948) described the Hargraves cell in its most characteristic form as a polymorphonuclear leukocyte which had engulfed a round, basophilic, homogeneous mass seemingly of leukocytic origin.

The inclusion body took the Feulgen stain for thymonucleic acid, supporting the hypothesis that the mass originated from nuclear material. Such L. E. cells were found in 4 of 5 cases of acute systemic lupus erythematosus by Haserick and Sundberg (JID 11 209 1948)

Plasma from the patie t mixed with bo e marrow from a normal individual induces the phenomenon of nucleolysis and agglutination (Hargraves: PSMMC 24: 234, 1949) a period of incubation of some 15 minutes or more being required. Haserick and Bortz (JID 13 47 1949) observed the production of alterations induced by the plasma of 4 patients when added t normal bone marrow the plasma incited chemotactic attraction of polymorphonuclear leukocytes around a peculiar acidophilic, amorphous mass, with from 2 t 10 PMN cells forml g the rosettes. Among the clumps were typical L.E. cells. Boil i g the pla ma destroyed it bility to alter the normal cells.

L.E. cells were found in the circulating blood in 3 cases of systemic lupus by Sundberg nd Lick (JID L 83, 1949) in the cantharides blister fluid in such cases by Watson et l (ADS 63 328 1951) and in the exalated pericardial fluid of one patient by Seaman an l Christensen (J 149: 145, 1952) The albuminuric urine of a febrile, arthritic patient also induced the phenomenon (Korting and Schmitz: DWchn 1.5 174, 1953)

The lytic factor in plasma from systemic l pus patients is associated with the gamma globulin fraction and is as hown by immunologic studies, different from normal gamma globulin (Haserick: JID 16: 311, 1951; J 148: 1318, 1952)

Passi e transfer via the placenta evidently occurred in a newborn whose mother suffered from systemic lupus, noted Bridge and Foley (AmJMedSci 227: 1, 1954) for the test remai ed positive in the infant for only a few weeks.

L.E. cell were found in several cases of rheumatoid arthritis and penicillin hypersensitivity by Weiss and Swift (AD 72: 103, 1955) who nevertheless felt that the pres-

ence of the typical L.E. cell may be taken as conclusive evidence of systemic L.E. They stated that Gomens had produced the Apresoline syndrome in dogs, so that an experimental animal may now be used in studying this challenging disease (see p. 170)

Quinacrine in a concentration of 10 mg per 100 cc. inhibits the formation of L.E. cells in vitro in weak serums, 40 mg. per 100 cc. in potent ones, reported Dubois (AD 71: 570 1955)

The stages of evolution of the L.E. cell were delineated by Stich et al. (ADS 65: 581, 1952): the nucleus of the polymorphonuclear leukocyte breaks down, fragments and undergoes phagocytosis by another PMN cell. A pre-L.E. cell stage may be observed when the defective nuclear material remains as yet within the boundary of the cell in which it originated. The L.E. cell results when this material has been picked up by another cell. One may find, then leukocytes containing ingested masses of smoky degenerated nuclear material (L.E. cells) or free nonphagocytosed masses identical with the material seen within L.E. cells or clusters of PMN cells about masses of cellular débris (Berman et al.: AmJClinPath 20 403, 1950)

Hematoxylin staining bodies were found widely distributed in 33 of 35 cases by Klemperer et al. (APath 49: 503 1950) like the bodies found by Gross in the endocardium and by Ginzler and Fox in the lymph nodes and kidneys in systemic lupus erythematosus. These bodies were similar to the vegetations found on the heart valves in the Libman-Sacks type of endocarditis. They consisted of a finely granular eosinophilic matrix in which were embodied clumps and packets of purple-blue bodies, ovoid or spindle shaped



Fig 1227.—The classic L. E. cell with engulfed, lysed, nuclear material is round, smooth, and rather poorly stained, and the entire chromatin pattern has been lost. This lysis, with loss of structure is the diagnostic feature of the phenomenon. (Dr M. M. Hargraves.)

Fig 1228.—The "rosett" of Haserick, showing smooth, poorly stained material and the agglutination of potential phagocytic cells about the mass of lysed chromatin, in a peripheral blood preparation. (Dr M. M. Hargraves.)

and structureless, sometimes coalescent to form large masses. Scattered through the pink matrix were polymorphonuclear leukocytes and mononuclear cells, many of which had bizarre or abnormally staining nuclei. Such bodies were not found in control material and appeared to be a specific structural criterion of lupus erythematosus. Histochemical studies indicated that they contained more or less depolymerized desoxyribose nucleic acid. Identity of the ingested nuclear material of the L.E. cell with the hematoxylin bodies of Klemperer et al. was accepted by Smith (BJD 64: 10 195-)

The L.E Cell Test.—Three ingredients are necessary if a positive test is to be obtained (1) the lytic factor present in the serum of the patient with systemic lupus (2) nuclear protein to react with the lytic factor and (3) viable phagocytic leukocytes to engulf the lysed material (Zimmer and Hargraves PSMMC 27 424, 1952)

Venous blood from 5 to 10 cc., is drawn from the patient and allowed to stand and clot at room temperature for from 1 to * hours. The clot is broken up by poking it with a wooden applicator stick, and the bloody serum is saved and spun at *000 r.p.m. for 5 minutes. Removing the top 1 cc. to a hematocrit tube one spins this again similarly and smears and stains the top layer which is rich in leukocytic material. Haserick (J 145: 16 1951) used either dog bone marrow or concentrated peripheral blood as the indicator. One adds 0.5 cc of suspected plasma to 1.0 cc. of bone marrow in a paraffined tube, agitates the mixture slowly for half an hour, removes it to a hematocrit tube to spin at 1,500 r.p.m. for 5 minutes, then smears the cellular layer and stains with Wright's stain. Rosettes of clumped leukocytes and/or typical L.E. cells are diagnostic when dog marrow is used

When one mixes blood from the patient and from a normal individual, centrifuges the mixture a d smears and stains the buffy coat one finds L.E. cells (Moffatt et al.: JID 14: 153, 1950) The material on the lide may be covered with Wright s stain for 90 seconds, then with a buffer for 2 minutes, following which, diluted Giemsa stain is used for 6 minutes, the slide then being washed with distilled water and dried (Barnes et al.: ADS 63: 771, 1950) The clotted blood technics are more sensitive than those using anti coagulants (Zimmer and Hargraves: PSMMC 27: 424 1952)

A modified method using peripheral blood was described by So pper and Nathan (JID 24: 472, 1955) who claimed for their technic profusion of L.E. cells and no false positives.

Interpretation of L.E Cell Test.—The value of seeking the L.E cell phenomenon as a diagnostic test is undoubted, as recognized by Haserick (ClevelandClinQuart 16 158 1949) L.E. cells were found in 14 of 21 cases of systemic lupus by Sukata and Conley (JLabClinM 37 597, 1951) in smears of the buffy coat obtained from heparinized blood, but not in any other dis eases such as periarteritis nodosa rheumatic fever thrombopenic purpura or dermatitis medicamentosa. Their formation was inhibited by low temperature and incubation at 37° C. for 15 minutes appeared adequate to allow optimum production of L.E. cells. Berman et al. (1950) confirmed the finding of such phenomena only in acute lupus and in no other disease of the so-called col lagen disease group Similar reports of specificity were made by Walsh and Egan (NEngJM 246 775 1952) Rohn and Bond (AmJMed 12 422, 1952) and many others.

The phenomenon can be demonstrated in acute lupus in the active stage and occa sionally in the subacute form, but th abundance of L.E. cells is greatest when the phase is most acute and tends to decrease or disappea during remissions, reported Barnes et al. (ADS 62: 771 1950) The patient s plasma induced the phenomenon when his dis ease was active but 4 months later when he was improved, it did not (Alterman and Lindau SouthMJ 43: 1046, 1950) In occasional cases L.E. cells have been found onl after the patient has been treated with ACTH (Haserick J 146: 16 1951; Michael et L: Blood 6 1059 1951; Marten: BMJ 2: 188, 1953) and L.E. cells may reappear in the peripheral blood while the patient is in remission.

Nuclear débris from leukocytes with glycogen adsorbed on the surface produced something resembling the L.E. cell phenomenon (Silve and Kuna: JID 19 231, 195.) Synthetic heparinoid substances, Liq oid and PVAS (a polyvinyl alcohol, polysulfuric acid ester) induce phagocytosis of polymorphonuclear leukocytic mat rial in the presen of serum, simulating the L.E. cell phenomenon, reported I te bitzin (JID 20 70, 1953) Penicillin intolerance productive of a f brile illness resembling serum sickness wa i 3 instances associated with the presence of th L.E. factor in the serum of these patients, reported Walsh and Zimmerman (Blood 8: 65, 1953)

Prognosis.—Hardly one-fifth of the patients remained alive 5 years after the diagnosis was made, reported Jessar et al. (AnnIntM 38 717 1953) in a survey of some 323 cases, of which 281 approximately 7 out of 8 were females. Polyarthritis is an indication of poor prognosis (Matras AfDuS 177 223 1938) Albuminuria is a constant finding in fatal cases, noted Madden (ADS 25 854 1932) and it is in the fatal cases that leukocytosis fails to appear even if terminal septicemia occurs. Persistent pyrexia and severe edema were earmarks of the fatal cases (O'Leary: MinnM 17 637 1934) Loss of weight is not marked until the disease is advanced. O'Leary reported 47 cases with 10 autopsies. Within 9 months after dissemination, 20 patients with the acute type were dead 8 of 27 patients with the subacute variety died within 4.5 years. Pneumonia was the great danger Bed rest, small transfusions, quinine Plasmochin and small doses of gold were measures used to the apparent advantage of 7 subacute cases by O'Leary prior to 1935

Pregnancy in relation to lupus erythematosus was carefully studied by Ellis and Bereston (ADS 65 170 1952) In the acute disseminated disease there occurred 25% maternal mortality and 30% fetal mortality In subacute disease the effect on the mother was slight but 46% of the fetuses were lost. Discoid disease had no influence on fetal or maternal mortality they found.

Surgical procedures, major or minor had no ill effects, reported Green house (ADS 67 456 1953)

The L. E. cell test (q v) seems to have fairly reliable prognostic value. Since it is quite reliably diagnostic of systemic lupus erythematosus, a positive test is to be interpreted to mean that the patient is seriously ill.

The effectiveness of cortisone and ACTH in palliative therapy has changed the outlook since 1950 in a disease which was previously only occasionally outlived by the patient recognized as suffering from systemic lupus erythematosus. *Newer concepts of the natural history of the disease with its remissions* and variations of severity encourage the belief that many patients survive for prolonged periods of time during which they are not extremely ill (Tumulty J 156 947 1954) The fact that the manifestations are protean was stressed by Sexton (JTennMA 47 405 1954)

Treatment.—It is dangerous to attack foci of infection, although they are usually present they should be eradicated, and this should be done with circumspection while the patient is in remission, if possible, and with adequate coverage by ACTH and cortisone therapy Transfusion usually fails to benefit.

Engman (ADS 35 685 1937) stressed the relation to fatigue and overwork, the occurrence of leukopenia, and the need for rest in the period of onset, which may be insidious bed rest cod liver oil and a nutritious diet are, he believed, especially valuable agents in combatting the disease.

Sulfonamides have been variously assessed: Weiner (ADS 41: 534, 1940) helped of 4 cases. Wile and Holman (ADS 42: 1069 1940) were discouraged by their experience with 7 cases. Penicillin seemed to cure the patient of Strakosch (ADS 54: 197 1946) but its effects are not reliable. Montgomery and McCreight (1949) knew at that time of no satisfactory treatment, sulfonamides and penicillin having proved ineffectual, they judged. Cannon (ADS 51 26; 64, 1945) was enthusiastic about the cures he claimed with 7% tincture of iodine given in increasing doses from 3 to 40 drops t.i.d. by mouth and supported by high calorie diet, vitamins and, perhaps, transfusions.

Liver extract by intramuscular injection was the recommendation of King and Hamilton (SouthMJ 34: 394 1941) who claimed 6 cures see Cornbleet (ADS 43 829, 1941). Sodium para-aminobenzoate seems to help in subacute disseminations (Zarafonetis et al: JID 11: 359 1948) Calcium pantothenate 200 to 400 mg daily and a bland ointment locally were recommended by Goldman (JID 11: 95 1948)

Vitamin E along with derivatives of pantothenic acid appeared to be helpful, thought Welsh (ADS 65: 137, 1952; 70 181 1954) The value of the tocopherols was denied by Morgan (BJD 63: 224, 1951)

Vitamin B_{12} in doses as great as 1,000 micrograms per day relieved systemic lupus erythematosus, promoting involution of skin *lesions* and elevating depressed levels of vibratory sensibility according to Goldblatt (ActaD-V 33: 216 1953; ADS 68: 737 1953)

Atabrine is not appropriate in acute systemic lupus erythematosus and may make it worse (O Leary GP 9 5 1954) Bed rest and B_{12} are best O'Leary thought. Atabrine failed to maintain improvement obtained with cortisone and ACTH in a case of Hesserick and Burdick (ADS 68 340 1953) Yet the cautious use of chloroquin has appeared to be beneficial in a few cases of mine; see Dubois (AIntM 94 131 1954)

Splenectomy may palliate in patients in whom threatening symptoms include thrombocytopenia, leukopenia and hemolytic anemia, thought Johnson (ADS 68 699, 1953). *Brunsting discussing this essay stated that the procedure is futile as a means of altering* the course of the disease.

Adrenal insufficiency symptoms were recognized by Gougerot (PresseM 43 1051 1935) in 3 cases with marked asthenia hypotension and tuberculosis he tried pluriglandular therapy using what was then available *Creatinuria* and low 17 ketosteroid excretion led Lamb et al. (ADS 57 785 1948) to give steroid hormones, which helped some females. While ACTH influenced the *condition favorably in 3 cases seen by* Plotz et al. (ADS 61 913, 1950) producing diminution of fever pain and inflammation benefits lasted only while the hormone was being given, and his patients died in spite of it. A like experience was reported by Whipple and Davidson (JLabClinM 36 206 1950)

Cortisone and ACTH produced similar remissions, *but the benefits of* ACTH were apparent within from 12 to 18 hours as compared with from 3 to 4 days with cortisone in the experience of Soffer et al. (AIntM 86 558 1950) Mucosal lesions healed within from 7 to 10 days, the skin was somewhat slower to respond, and retinal hemorrhages in 5 patients resorbed *in from* 2 to 3 weeks. The patients relapsed within 5 or 6 days when the hormones were

withdrawn After maintaining control for several weeks with the drugs, the dose was reduced to that which was sufficient to hold the remission. Suppression of the disease with cortisone was successful in 4 patients, but 3 died in spite of its use reported Brunsting (PSMMC 25 470 1950) and while benefits from cortisone and ACTH were striking they were temporary and produced no significant improvement in the characteristic laboratory phenomena of the disease, according to Brunsting et al. (ADS 63 29 1951)

Only 1 of 16 patients of Haserick et al. (J 146 463 1951) could not be controlled, for full doses succeeded during the crises in most patients and thereafter small doses were sufficient. Of 18 cases in which treatment was continued for from 3 to 20 months, 6 patients died, 8 were obliged to continue medication, and 4 appeared to be cured (Soffer and Bader J 149: 1002, 1952)

The potential ill effects of cortisone and ACTH require watchful supervision, and medication may have to be discontinued because of ascites or psychosis (Johnson and Meyer AmJMedSci 223 9 1952) Yet cortisone and ACTH represent a magnificent improvement over therapy previously available even though they sometimes fail and usually only palliate (Haserick ADS 68 714 1953) They fail particularly in patients with progressive renal disease Thanks to cortisone and ACTH, not one died of the 16 patients of Cohen and Cadman (Lancet 2 305 1953)

See Scholtz (ADS 6: 467 1922) types of dissemination: gradual, with or without subsidence and acute with erysipelas-like or erythema multiforme-like rashes, sometimes hemorrhagic, and chills, fever prostration, death; focal infection can initiate disease Goldstein and Wexler (AOphth 8 852, 1932) ocular manifestations; Keil (ADS 28 765, 1933) 100 cases Garfield et al. (ADS 30 172, 1934) hemorrhagic case made worse by gold and by erysipelas antitoxin; Baehr, Klemperer and Schifrin (TransAssnAmPhys 50: 139, 1935 51 43, 1936) diffuse peripheral vascular lesions in 23 autopsies, 13 with verrucous endocarditis Denzer and Blumenthal (AmJDisChild 53: 525, 1937), girl 7 years old, autopsy; Anderson (ADS 34: 621, 1936), fulminant case following sunlight exposure cured by sulfonamide; Jadassohn (ADS 39 792, 1939) review of systemic lupus, Senear-Usher syndrome, Libman-Sacks disease and Osler' erythema group; Urbach and Thomas (BJD 51: 343, 1939) types of lupus, for which authors preferred Jadassohn' name, "erythematodes"; Contratti and Levine (NEngJM 221 402, 1939) tried sterilization with x ray therapy autopsy; Humina (AnnIntM 13 1209 1940) case exemplifying wide assortment of manifestations; Downing and Messina (NEngJM 227: 402, 1942) onset with pernio-like lesions of fingers followed by dissemination; Gunn and Adams (AmJMedSci 205 33, 1943) 4 cases in young women with nephrosis and fibrinous pleuritis and pericarditis, autopsies; Fox (APath 36 311, 1943), onset following antitoxin; Claxton and Krause (AnnlM 19: 642, 1943) 4 cases, 2 in Negresses, treated with rest, urine care, transfusions, elimination of foci and x-ray directed at ovaries; Smith (MPract 210 246, 1943) treatment with rest, transfusions, sulfonamides and quinine; Pearson (BMJ 1 253, 1944), case recovered on transfusions, sulfonamide, Pentnucleotide and sulfonamide; Hoffman (ADS 51 190, 1945), sulfonamide intolerance simulating acute lupus Koch and McGuire (AmJOphth 29: 1243 1946) exudative and hemorrhagic chorioretinitis, intraocular manifestations; Ayvazian and Badger (NEngJM 239 565, 1948), 3 fatal cases among 750 student nurses, lupus being second to tuberculosis as major cause of death in this group; Mitchell and Goodwin (ADS 58 512, 1948) apparent benefit from penicillin Beare (BJD 61 232, 1949) 6 cases of "malignant lupus, with pathologic similarities to polyarteritis nodosa and acute rheumatic fever all of which may represent faulty reaction to unidentified antigens"; Curtis and Horne (AnnIntM 30 209, 1949) rare massive pericardial effusion in 2 cases; Arnold (BJD 61 185, 1949; ADS 62 632, 1950) "systemic" preferred to disseminated" Silver et al Haserick, Graeff, Rein and Kostant, Pascher Piotz et al. (ADS 61: 667 ff, 1950) lupus erythematosus of all types, clinical, etiologic, laboratory therapeutic aspects; Johnson et al. (JID 14: 205, 1950), chloramphenicol useless; Edit (J 146 819 1951) plasma L.E. test; Fernandez (abs J 148: 1561, 1952) 12 Argentine cases, palliation with cortisone and ACTH; Griffith and Vural (Circ 3: 492, 1951) 18 autopsies in cases with polyarthritis, fever and tachycardia, urinary abnormalities, leukopenia and serosal inflammation of unknown cause as the most common manifestations; Pastor et al. (NEngJM 244 81, 1951) 36 Philadelphia Gen. Hosp. cases in 1938-1949 10 of which were males, arthritis an early feature often mistakenly diagnosed at first; Shearn and Pirofsky (AlntM 90: 790, 1952) 34 cases, 31 female, ages 3 to 58 years, antecedent actinic exposure in 18 of 31 with skin lesions, abnormal EKG in 21 of 29 L.E. cells in 29 of 31 tested, 20 treated with cortisone and ACTH with encouraging effect in only 14, 4 deaths during therapy with these drugs; O'Leary et al. (PSMMC 27: 405 ff, 1952) symposium, current review; Heptinstall and Sowry (BMJ 1: 525, 1952) peripheral neuritis the presenting symptom, autopsy, Shearn and Pirofsky (ArchIntM 90 790, 1952), 34 cases, 14 deaths in from 7 weeks to 20 years, 4 while on cortisone ; high incidence of transfusion reactions; Jessar et al. (AnnIntM 38 717 1953) 44 cases and review 16 necropsies with 12 showing kidney disease; 32% lived longer than 5 years; Gold (BJD 65: 43, 1953), diagnosis depends on clinical judgment; Gold and Gowing (QuartJM 22: 457, 1953), review 16 cases, 7 autopsies, disease process resembles antigen-antibody reaction, Marles and Blackburn (JClinPath 6, 59, 1953) demonstration of L.E. cell; Edit (SouthMJ 46 297 1953), L.E. cell; Lindau (SouthMJ 46 1099 1953) subacute in Negro male, autopsy; Rosenfeld et al. (J 155: 666, 1954) L.E. cell demonstration in blood from finger puncture; Ellis and Hundley (ADS 70 311, 1954) histology of discoid and systemic L.E. distinct; Michelson (ADS 69: 604, 1954) stimulating essay; Dubois (CalifM 80 154 1954) cytologic diagnosis Soffer et al. (ArchIntM 93 503, 1954) cortisone and ACTH treatment, 24 cases Dubois (ArchIntM 93: 667, 1954), nitrogen mustard therapy in desperate cases, unpredictable Richards (BMJ 2 777 1954), 3 cases well maintained by cortisone, with dramatic effect on acute episodes; Matthews and Maxwell (BMJ 2: 1140, 1954) pulmonary manifestations predominating, benefit with ACTH; Harvey et al. (Medicine 33: 291, 1954) clinical analysis of 138 cases.

BULLOUS DERMATOSES OF UNDETERMINED CAUSE

DERMATITIS HERPETIFORMIS

Symptoms—Dermatitis herpetiformis (Duhring s disease) is a chronic, relapsing inflammatory dermatosis characterized by the occurrence of erythematous papular vesicular or pustular lesions, which tend to be grouped, are intensely itchy and are followed by pigmentation and atrophic scarring An attack is usually ushered in by slight constitutional symptoms, seldom severe but in many patients serving as an aura. Itching is exceedingly distressing Sensations of burning and tension also are frequent complaints The vesicular form of eruption is the most characteristic but polymorphism is common. The eruption, roughly symmetric nearly always involves the sacral triangle and the scapular areas. The scalp and extensor aspects of the extremities are usually affected. The lesions develop rapidly in groups and circles which spread by peripheral extension. The vesicles possess thick, tough walls and seldom rupture spontaneously The patient finds relief in scratching off their tops preferring pain to itching Scarring and pigmentation are characteristic sequelae

The disease is a variable and erratic one Periods of outbreak are interspersed with periods of comparative quiescence. Victims become nervous, poorly nourished, debilitated exhausted and despondent as a result of itching and loss of sleep

No age is exempt for the patient of Ebert (ADS 48 210 1943) was 3 years old, and that of Wilson (ADS 44 58 1941) only 2 weeks see Sutton (AmJMedSci 140 727 1910) Oliver and Eldridge (J 77 945 1922) In children the vesicular and bullous forms are usual. While the peak incidence seemed to Goodman (ADS 43 248 1941) to be around age 60 the vesicles were smaller in his young patients. Multiformity of eruption, grouping of lesions and pigmentation are not necessarily found in children (Knowles JCutD 25 247 1907 Evans BJD 61 89 1949)

Localized dermatitis herpetiformis has been recognized by some (Andrews ADS 50 68 1944) but I agree with Stümpke (MedKlin 35 1399 1939) regarding the systemic nature of the disease and have never identified a localized instance

Herpes Gestationis appears to be true dermatitis herpetiformis, peculiar only in its concomitance with pregnancy stated Howard (ADS 28 762, 1933)

> A typical attack is ushered in with generalized pruritus of greater or less severity Then there appears a patchy erythema, starting as a rule on the extremities and sometimes on the trunk. Within a day or two the erythematous areas enlarge, while small vesicles appear in herpetiform crops, arcs or rings. In one place or another the vesicles are to be found entirely surrounding a red macule or slightly raised and edematous plaque either t its junction with the normal skin or alined on a palpably elevated margin. Some vesicles coalesce to form tense, thick walled bullae of assorted sizes. At this time some of the bullae may be discovered arising from apparently unaltered skin. Later a few of the bullae become pustular or hemorrhagic. Following rupture the serous crusts eventually fall away leaving as a rule, only a distinct pigmentation. Mucosal lesions are decidedly rare. As the pregnancy progresses, periodic exacerbation are the rule, accompanied by mild to severe constitutional symptoms, such as fever dyspepsia, constipation, albuminuria and neuralgic pains.
>
> The prognosis for the mother is good. Sometimes there are sequelae consisting of periodic bullous effloresce ces, usually diagnosed as herpes menstrualis recidivans. A few cases with serious or fatal outcome have been reported. In one instance in particular long series of successive pregnancies led to attacks of greater and greater severity until the patient finally succumbed with ulcerative lesions of the mouth, esophagus and colon, thus sim lating a pemphigus. On the other hand, Ward s case was one n which a gestation had occurred yearly for eight years with no serious consequences. The outlook for the child is much less hopeful than that for the mother

While the onset is oftenest during the fourth to fifth month of pregnancy cases have been recognized as having started during the puerperium. The disease was seen accompanying chorioepithelioma (Elliott ADS 37, 219

Fig. 1229.—Dermatitis herpetiformis, severe, in a Kansas farmer.
Fig. 1230.—Dermatitis herpetiformis, acute exacerbation.



Fig. 1231.—Dermatitis herpetiformis.

1938) and in a similar case with positive Friedman test x ray therapy which reduced the cancer was followed by disappearance of the rash (Tillman BMJ 1 1471, 1950) In the patient of Cawley et al. (SouthMJ 46 827 1953) a possible relation to Rh isosensitization was possibly of etiologic significance.

Etiology—The cause is not known. Dermatitis herpetiformis is comparatively rare, affecting oftenest adult males. Most of my patients have been out door people who have had considerable association with domestic animals. Michelson (ADS 50 68 1944) stated that most of his patients were farmers. I unsuccessfully tried to locate animal parasites on this account and in view also of the eosinophilia (Leredde and Perrin AnndeD 1896 pp 281, 369 452) which is usually present the response to various parasiticidal medicines, and the resemblance of symptoms to those of craw-craw (p 590)

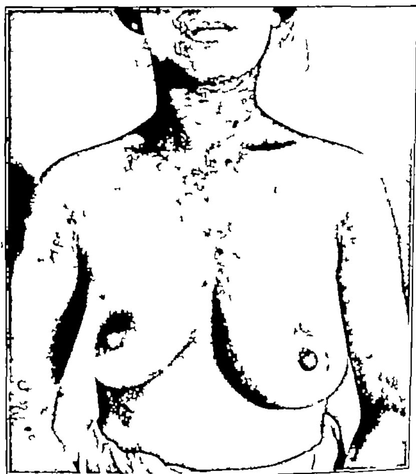


Fig 1232.—Dermatitis herpetiformis. (Drs. John Fordyce and George Mackee)

Sensitivity to iodide was noted in sufferers with dermatitis herpetiformis as early as 1892 by Besnier and Doyon, while Jessner and Hoffman in 1925 found them intolerant of bromides, according to Sulzberger (JAllergy 7 385, 1936) who quoted Merfert as having reported that, in 13? cases, 86% gave positive reactions to patch tests with bromide or iodide while in pemphigus no such sensitivity exists. The sensitivity may be dispelled by the intravenous injection of sodium thiosulfate according to Jaffé (abs YBD 1930 p 91) Felsher (JID 8 55 1947) noted that patch tests with 20% potassium thiocyanate in petrolatum are also positive and recognized the phenomenon as being due to the swelling of gelatin so as to induce separation of the epidermis by salts of the Hofmeister series. Positive patch and intradermal tests with

a pneumococcus from the patient s bronchial secretion were obtained by Calla way and Sternberg (ADS 43 956 1941) and comparable allergy to a *B coli* vaccine was studied by Swartz and Lever (ADS 47 680 1943)

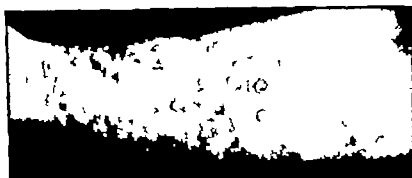


Fig. 1232.—Dermatitis herpetiformis. (Dr Sam Sweitzer)





Fig. 1233.—Dermatitis herpetiformis in child. (Dr Isadore Dyer)
Fig. 1234.—Dermatitis herpetiformis, a common distribution

There has been much written, but little proved, regarding the hypothesis of virus etiology especially by authors who are confused as to the distinctness of derm titis herpetiformis nd pemphigus. Gla bersohn (PrzeglD 29: 265, 1934) found that bliste fluid given i tradermally i to the patient himself provoked a blister; given into a control kin, only erythema resulted. Blister fluid mixed with the patient's blood serum provoked no blister Bedson (BJD 47: 140 1935) and Urbach and Wolfram (ADS 33 789 1936) ha e each found viruses, neither I think, meriting much credence. See Pemphigus,

etiology Cases have followed vaccination, in which it is conceivable that an unwanted virus was accidentally inoculated (Pusy: JCutD 15 158 1897; Bowen (JCutD 19: 401 1901 22: 265 1904; 23: 381, 1905)

The serum proteins, especially albumin, are generally reduced (Turpin and Chassagne AnndeD 10: 862; 969 1939)

The one autopsy of which I know was reported by Turpin et al. (PresseM 47: 821, 1939) who found an enlarged liver with periportal fatty degeneration.

Electron micrographs made by Everall and Reed (BJD 65: 432, 1963) showed mis shapen and shortened collagenous fibrils and excessive dermal material in the lesions and also in the apparently unaffected skin. In pemphigus no such alterations were found.

Diagnosis.—The disease is to be differentiated from pemphigus (q v) erythema multiforme infectious eczematoid dermatitis, scabies, and pedic ulosis In scabies interdigital spaces are likely to be involved while the scalp is unaffected lesions are minute blood-capped, excoriated papules itching is worse at night and the patient s associates are usually infected.

Prognosis.—An attack can usually be ameliorated or stopped but perma nent relief can never be promised. The outlook is better in younger patients. Follow up for a period of 34 years in 21 cases having their onset in childhood was reported by Søbye (ActaD V 26 561 1946) 10 had been symptom free for 20 years while 11 remained uncured he judged the average duration of the disease to be some 20 years. Of 105 Edinburgh Royal Infirmary cases seen



Fig. 1136.—Subepithelial vesiculation in dermatitis herpetiformis. (Dr Stuart C. Way)
Fig. 1137.—Dermatitis herpetiformis.

in 6 years, 64 were males, 41 females and of 42 followed for a long time 16 ceased to manifest the affliction 7 remained relatively quiescent, and 19 stayed active reported Peterkin (BJD 63 1 1951) Data on 381 patients, comprising about 0 5% of Mayo Clinic dermatologic cases, were gathered by Eyster and Kierland (ADS 64 1 1951) Males were affected 2.7 times as frequently as females. The age at onset ranged from 6 months to 78 years. There was a decided tapering off of intensity after the disease had existed for 10 years or more Sensitivity to halogens was not sufficiently constant to be of diagnostic value. Patients who had long taken Fowler s solution frequently showed chronic arsenic intoxication. Follow-up studies on 53 cases by Everall (ActaD V 34 259 1954) suggested that the disease lasts for 5 or 6 years on the average yet I hesitate to tell my patient when he will be cured

Treatment.—The patient must obtain rest. This can often be obtained by interdicting coffee by giving aspirin, gr v every 3 hours and by urging him to lie down when he is not obliged to do otherwise. Bromides and iodides must be avoided

The best internal medication is a sulfonamide sulfapyridine being pre ferred by Costello (ADS 42 161 1940 56 614, 1947) A small dose may suffice. While due precaution as to possible ill effects must be taken, the pa

tient of Barling (Lancet 1 503 1944) ingested sulfonamides for over 3 years with relief and one patient of Costello (1947) took sulfapyridine for 7 years without ill effects.

Diasone a substituted diaminodiphenylsulfone invented by Raiziss (Sci 98 350 1943) and of value in the treatment of leprosy was found valuable in dermatitis herpetiformis by Cornbleet (ADS 64 684 1951) an observation subsequently amply confirmed. My associate Bernard Winston, tested the drug during 1949 but did not report its effectiveness in our patients. The dose is 0.3 Gm t.i.d. or less undertaking to use the smallest amount that will control the symptoms. Periods of respite from the drug are required of the patient who sometimes remains free once the symptoms have abated, for several weeks or months without medication. Some patients must take 0.3 to 0.6 Gm daily over a long period of time. The ill effects on the red blood cell or white blood cell count and on hemoglobin concentration must be watched for continuously If the patient does not respond to Diasone within a few weeks, benefit from its use may not be hoped for

Acetosulfone (Promacetin) was considered to be almost as effective as sulfapyridine and equally safe by Costello and Buncke (AD 72 348 1955) The dose may be 3 or 4 Gm. daily until remission is obtained thereafter 2 Gm per day Since hypochromic anemia develops in many patients, iron should be given also but Costello and Buncke did not observe real toxicity In 12 cases, they obtained complete remission in 8 and control in 2.

Focal infection should be eliminated (tonsillectomy cured, for example the patient of Irvine JCutD 36 64 1918) Autogenous vaccine made from organisms obtained from a focus has been tried by Callaway (SouthMJ 35 415 1942) but I should judge this measure unlikely to be remunerative

Quinine, autohemotherapy thiosulfate intravenously and hyperpyrexia may be tried. Emetine was found helpful in patients with pyorrhea (E gman and Davis J 66: 492, 1916) I obtained some benefit in 2 cases with Fuadin, but a trial of Hetrazan wa f ll re Roussel (ADS 31: 566, 1935) gave chromium sulf te, gr iv t. i. d., medication which must not be administered with alkali. H claimed for th drug a specificity which is not of common observation, though benefit has at times seemed to result. Alderson had good results with hyperpyrexia by means of baths. Sodium thiosulf t intravenous was said t have cured 4 patients of Steiner (DWchn 93: 692, 1934) Penicillin has been reported to have helped the disease temporarily (Lain ADS 5_: 84, 1945) but the pa tie ts of Carpent r and Hall (ADS 51 41 1945) relapsed when it was st pped.

Sodium cacodylate is particula ly valuable. Doses of 0.5 Gm, ntramuscularl or intravenously may be given twice a week duri g the necessary time. Iron cacod late 0.065 Gm. pe day for a long time, was recommended by Weiss.

Acetarso e, 0.5 Gm./day for 3 days a week, may relieve (Cornbleet et al.: ADS 5_: 292, 1946) Niacin a doses of from 50 to 200 mg. q.i.d. was sometimes helpful reported Johnson and Blakley (JID 14: 233, 1950) Para-aminobenzoic cid produced partial or complet suppression of the eruption in 16 cases of Zarafonetis et al. (ADS 63: 115 1951) but all relapsed within 10 days when the drug was withdrawn.

Locally calamine lotion, to which has been added 0.5 to 2% carbolic acid and 1 to 5% compound tincture of coal tar alleviates. Duhring recommended an ointment containing 5 to 10% sulfur

In herpes gestationis, no treatment could be found that was helpful t the 3 patient of Mueller and Lapp (AmJObGyn 48: 170 1944) Abortion may be justified if the disease has manifested increasing severity in successive pregnancies (Bruns DMedWchn 64: 256, 1939) Autohemotherapy has been recommended (Ormsby, quoted by Costello NYStJM 41: 849 1941) Sulf thiazole helped Lewis's patient (ADS 46: 841, 1942) but that of Turne et al. (AmJObGyn 41: 525 1941) was unresponsive to medicines yet healed promptly aft parturition. In 10 cases of polymorphic itchy eruptions occurring d ring pregnancy progesterone in doses of from 25 to 50 mg daily was followed by remission, and normal infants were delivered at t rm, reported Kenty et al. (ADS 63: 675, 1951) Corti sone i sometimes dramatically beneficial. In a patie t who suffered herpes gestationi during several pregnancies, sulfapyridine was beneficial t first but yielded little response later nd during the fourth pregnancy, while cortisone produced som improvement, it was ACTH which accomplished n excellent palliation, reported Lindemann et al. (AmJ ObGyn 63: 167 195_) ACTH cured a patient of Zakon et al. (ObGyn 2: 78, 1953)

The lack of value of ACTH and cortisone in dermatitis herpetiformis makes one suspect that this disease and herpes gestationis are quite different.

See Duhring (J 3:225, 1884; AmJMedSci 1884 p. 93 Selected Monographs on Dermatology New Sydenham Soc., London, 1893, p. 179) Brocq (AnndeD 9 1, 65, 133 209 301 434 493, 1888); Jamieson (BJD 10 73 118 1898), Engman and Mook (JCutD 24 214, 1906) indicanuria in dermatitis herpetiformis; Lieberthal (JCutD 28 463, 1910), review, Alderson (ADS 33:468, 1936) fever therapy with hot baths, Oliver and Cohen (ADS 44 262, 1941) apparent cure with sulfapyridine Madden (ADS 47 698, 1943) sulfapyridine caused drug eruption Swartz and Lever (ADS 47 680 1943), etiology Lady (ADS 49:362, 1944) 8-year old patient, utility of sulfonamides, Park (BJD 57 161, 1945) failure with penicillin, relief with sulfapyridin, DeOreo (ADS 54 360 1946) twins affected, Welsh (JID 10 221, 1948) streptococcus in etiology Gorden and Loewenthal (BJD 61 355, 1949) relation to chronic eczema Robinson et al. (JID 13 9 1949) Aureomycin beneficial Shaw (JID 14 3, 1950) Aureomycin and chloramphenicol worthless, Kanter et al. (ADS 62 422, 1950) response to Terfonyl after failure with sulfapyridine Phillips (BMJ 1 1241 1951) failure with Aureomycin, success with arsenic Philpott et al. (JID 18 87, 1952), vasodilator Roniacol tartrate helpful, perhaps because of pyridine radicle Hopkins (BullJHH 92 1, 1953) 13 year experience with sulfonamides, sulfapyridine best Hollander (ADS 70:362, 1954) smallpox vaccinations helpful.

IMPETIGO HERPETIFORMIS

This rare and usually fatal disease first described by Hebra (WienMWehn 32 1197 1872 Lancet 1 399 1872) is manifested by a symmetric eruption of pustules which occur in crops, form groups or rings with flat yellow crusts but without ulceration itch little if at all and are accompanied by severe constitutional symptoms The lesions are pustular from the start, being never vesicular The pustules and the blood are sterile on culture The eruption may become widely disseminated. Fever great prostration, leukocytosis, hypocalcemia and sometimes tetany accompany it. When the lesions heal, an unusual reddish brown pigmentation is seen.

Most patients are pregnant females (Carter and Pearse AmJObGyn 33 114 1937) The child when born is free of the eruption but dies soon (Tenlen ActaD-V 18 165 1937) The reviews of Hall (ADS 50 107 1944 Lancet 1 509 1944) should be consulted the patient he reported was a man whose dermatosis followed lobar pneumonia and healed under sulfonamide therapy Anderson, discussing Hall s paper would segregate a group of cases not associated with pregnancy but occurring usually subsequent to a severe infection in a seriously toxic patient with a septic fever

Parathyroid extract or vitamin D concentrates such as dihydrotachysterol may be given with hope of benefit (Scherber DWehn 106 361, 1938) Although a woman in her fourth month of pregnancy reported by Frank (ADS 40 253 1939) was saved by sulfanilamide her twin infants were promptly aborted. Sulfathiazole was curative in the male patient of Teodorescou and Conu (AnndeD 7 250 1947) A woman who suffered 4 attacks was castrated by x ray therapy and thereafter remained free of the disease (Cedercreutz ActaD V 40 403 1939) A patient who had relapses during each of 6 pregnancies was kept symptom free by gonadotropic hormone in doses of from 750 to 6 000 units (Thyresson ActaD-V 28 507 1948) Aureomycin yielded dramatic improvement in the male patient of Sheard (ADS 64 64 1951) as it might have had it been available in a patient with staphylococcic pemphigus acutus who died under the care of Robinson (CalifWM 45: 497 1936)

PEMPHIGUS

Symptoms.—Pemphigus is a rare serious dermatosis characterized by the eruption of successive crops of bullae which develop suddenly often on apparently normal skin. Clinically true pemphigus may be separated into 3 types pemphigus vulgaris pemphigus foliaceus and pemphigus vegetans.

Pemphigus Acutus occurs especially in those who are occupationally liable to infection from animals and their products. *The outcome may be fatal.* The bullae range in diameter from 1 to 10 cm. and may contain a mixture of blood and serum. Coalescence and abrasion result in the formation of large painful denuded areas. See Staphylococcic Impetigo of which acute pemphigus is one variety

Pemphigus Vulgaris.—The history of pemphigus was interestingly reviewed by Lever and Talbott (ADS 46 800 1942) The classification of Brocq (Ann

deD 7: 449 1918) separated bullous diseases into the acute form the foliaceus and vegetans forms, and true chronic pemphigus, which last he subdivided into malignant and benign varieties (see Lane and Lambert: ADS 4 141 1921)

In true pemphigus of the malignant form the patient presents the general appearance of marked prostration and is immobilized because of the severe pain elicited by movement. Both skin and mucous membranes are involved. On the sites of broken bullae, denuded, moist, sanguinolent surfaces rapidly appear and extend progressively at the edges with detachment of the horny layer of the skin and exhibit no tendency to heal. The prognosis is bad.

The onset in the usual patient is likely to be insidious with the development of blebs in a localized region, sometimes mucosal (Oppenheim and Cohen ADS 46 201 1942) A faintly erythematous and edematous rash with marginate lesions resembling urticaria but almost asymptomatic and less inflammatory may comprise the background upon which the noninflammatory bullae



Fig. 1222.—Pemphigus vulgaris. (Dr D. E. H. Cleveland)
Fig. 1223.—Pemphigus vulgaris. (Dr T W Thorndyke)

develop The local patch may be eczematoid. A widespread eruption of bullae ensues. Lesions may be present practically all the time, new blebs developing as the older bullae dry up and disappear or outbreaks lasting a few weeks or months are alternated with periods of complete or comparative quiescence. The bullae are 1 to 10 cm in diameter several in number thin-walled, translucent, sometimes coalescing They may be umbilicated or iris-like. Zeisler (JCutD 36 577 1918) found bullae to be flaccid in the serious cases and tense in the milder ones. They develop suddenly on apparently normal or slightly reddened areas increase in size little if at all, and are never infiltrated. The distribution of the eruption is roughly symmetric. Areas subject to friction are the sites of predilection.

Adhesion between the epidermis and dermis is damaged by subepidermal vacuolation, and an accumulation of fluid pushes off the epidermis. This seems to be due to a lipoproteinous change in the superficial collagen (MacCardle et

al ADS 46 517 1943) Pinching and friction provoke such separation. The Nikolski test consists in so traumatizing the skin as a diagnostic procedure its original description was quoted verbatim by Goodman (ADS 68 334, 1953) Bullae appeared where hyaluronidase was injected into the skin of a patient, but not where saline or heated hyaluronidase was injected (Grass JID 13 221 1949)

The mucous membranes seldom escape. The prognosis is better when mucosae are not involved.

Familial incidence of pemphigus vulgaris has been noted. A woman and her brothers died of the disease reported Granirer (ConnMJ 1 623, 1949) see Feldman (ADS 33: 730 1936) Greenbaum (ADS 41: 1073, 1940) Miller and Frank (ADS 89 494, 1940)



Figs. 1240 annd 1241.—Pemphigus vulgaris, acute in onset. See Fig 1242.

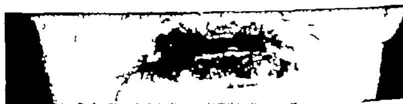


Fig 1242 —Pemphigus [vu]lgaris, lips of patient of Fig. 1240 Oral lesions appeared first in this case.

In a review of 100 cases, Combes and Canizares (ADS 62: 786 1950) observed that the location of initial lesions was, in order of frequency the mouth scalp, abdomen and chest. The mouth was the initial site in 25% of 114 cases reviewed by Lever (AmJOrthodont 8 509 194_) and 62 of the 114 cases showed oral lesions at some time All patient with vegetative pemphigus had oral lesions, 85% of those with acute disease 49% of those with chronic pemphigus 4% of those with foliaceous pemphigus, and none with pemphigus erythematodes. Lever believed that the presence or absence of oral lesions had no bearing on prognosis. Conjunctival lesions were found in 81% of his cases.

Itching may be considerable The patient loses strength and becomes an exhausting nursing problem. Decaying epithelium stinks, and secondary infection, *often terminating in bronchopneumonia*, takes its toll.

PEMPHIGOID.—Cases with bullae beneath an intact epidermis were so classified in contrast with cases accepted as pemphigus in which the bullae were apparently formed within the epidermis by acantholysis, by Rook and



Fig. 1243.—Pemphigus vulgaris. (Dr D. E. H. Cleveland.)



Fig. 1244.—Pemphigus vulgaris (Dr Gustav Riehl.)

Waddington (BJD 65 425 1953) in a study of 54 patients with bullous disease Of these 38 were pemphigoid and 16 pemphigus as differentiated by this criterion.

Of the pemphigoid cases, 13 died after an average duration of illness of 1 / 5 months. The course of the disease was more variable than in pemphigus with its more uniform evolution. The bullae sometimes remained localized to the sites initially involved. There were only single attacks lasting for from 3 weeks to 5 years in 8 of the patients who underwent eventual complete remission, although some patients had no significant remissions, while others had recurrent attacks alternated with complete remission.

Similar distinction between true pemphigus and chronic benign pemphigus was made independently by Brennan and Montgomery (JID 21 249 1953) in a study correlating clinical and histologic findings in 503 Mayo Clinic cases of bullous dermatoses. The location of the bullae in the nonacantholytic group was intraepidermal or subepidermal or both. Prickle cells did not show degenerative changes, and intercellular bridges were present, although because of pressure phenomena some of them might be ruptured, a process named desmorrhexis by Brennan. They concluded that forms of true pemphigus, such as pemphigus vulgaris, vegetans, foliaceus and erythematodes, are capable of simulating clinically other conditions of less serious prognosis, and vice versa, but that his-



Figs 1245 and 1246—Pemphigus erythematodes.

tologic distinctions could be made from such conditions as chronic pemphigus, familial benign pemphigus and other bullous dermatoses. They adduced evidence that the course in cases without acantholysis was benign as compared with the course when acantholysis was present.

Intraepidermal and subepidermal bullae may occur simultaneously in a bullous disease thought Prakken and Woerdeman (BJD 67 92, 1935) whose 60 bullous cases included 19 of pemphigoid, a name they considered inadvisable. They would give greater diagnostic emphasis to the clinical picture than has been fashionable recently.

Pemphigus Erythematodes is the name Ormsby (ADS 4 234 1921 Diseases of the Skin Lea & Febiger 1948 p 451) applied to the uncommon and relatively benign syndrome which Senear and Usher (ADS 13 761 1926) described as resembling lupus erythematosus on the scalp and face with discoid patches and carpet tack scaling and resembling seborrheic dermatitis on the trunk with congestion, flaccid bullae and crusting. New bullae appear and older lesions are tediously impetiginoid. Exacerbations and remissions mark the chronic and relatively benign course.

Wise told me that, having watched 2 such patients develop pemphigus vulgaris, he was convinced that the syndrome is a variant of pemphigus, not of lupus erythematosus. Wile and Arnold (ADS 40 687 1939) placed it as perhaps an entity sometimes identifiable only after prolonged observation.

The distinction of pemphigus erythematodes from bullous lupus erythematosus may be difficult (Wise: MedJRec 134 227, 1931; Kreibich ZentralblfHuG 30 16, 1929; Gilman: ADS 24: 84, 1931; Taussig: ADS 37: 498, 1938; Keil ADS 36: 748, 1937) The disease may respond to acetarsone (Zakon ADS 48: 232, 1943)

In a survey of 12 cases Griveaud and Achard (AnndeD 9: 120 1949) averred the prognosis is serious as in pemphigus, and noted a possible explosive course although this may pursue the benignity and chronicity of dermatitis herpetiformis. Histologically they found intraepidermal bullae and acantholysis. Senear and Kingery (ADS 60: 233, 1949) reconsidered the difference of opinion in the literature of 22 years, and stated that cases presenting a combination of elements suggestive of lupus erythematosus, seborrheic dermatitis and pemphigus are likely to prove to be examples of pemphigus erythematodes. At different periods in one case, there may occur confusion even with psoriasis, impetigo

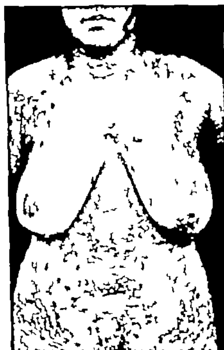




Fig. 1 47.—Pemphigus foliaceus (Dr A. R. Cannon)
Fig. 1248.—Pemphigus foliaceus.

or eczema. While the course is usually benign, the clinical picture has been known to change indeed, into that of pemphigus foliaceus vulgaris (Arnold and Johnson BJD 66: 18, 1954) It is exceptional, however for a case of the vulgar or foliaceous type to change to pemphigus erythematodes. Arnold and Johnson believed the histologic findings entirely distinct from those of lupus erythematosus. They confirmed the name given by Ormsby preferring to allow Senear Usher syndrome to be dropped.

Case reports include those of Wile and Belote (ADS 40: 678, 1939) Hedge (ADS 49: 330 1943) Beall (ADS 53: 490 1943) Vero (ADS 60 964, 1949)

Pemphigus Foliaceus may be more or less characteristic from the beginning or it may commence with resemblance to pemphigus vulgaris, herpetiform dermatitis or even exfoliative dermatitis. Large fragile flaccid bullae develop rapidly They contain pus from the first. They soon rupture, leaving a moist raw surface covered with seropurulent fluid. Decaying epithelium and exudation give rise to a peculiar sickening odor The course is essentially chronic Exacerbations followed by periods of comparative quiescence are common, but the skin seldom clears between attacks.

In pemphigus foliaceus, the degenerative epithelial changes seen in pemphigus vulgaris are present but are located more superficially. In older lesions, hyperkeratosis and degenerative changes of granular cells may result in changes reminiscent of those seen in Darier's disease (Lever ADS 64 777 1951)

Pemphigus Vegetans, more common in females, begins with eczematoid, impetiginoid or bullous disease generally of the axillae, groin, umbilical region mouth or pharynx (Riordan ADS 53 652, 1946) The genitals, chest, abdomen and other regions of the body may become involved. Some lesions persist, and papillary excrescences resembling condylomas spring up. Ulceration may occur. Belisario (1937) said that potassium antimony tartrate injections cure this disease.

A histologic study was presented by Director (ADS 66 343 1952) who found the lesions characteristic and, in conjunction with the clinical picture fairly diagnostic. Histologically pemphigus vegetans is basically similar to pemphigus vulgaris acantholysis occurring low in the epidermis, but modified by epidermal hyperplasia.

A malignant (Neumann) and a benign (Hallopeau) form were distinguished by Lever (ADS 64 727 1951) In the malignant variety early lesions are bullae resembling those of pemphigus vulgaris, while later lesions show epidermal hyperplasia with intraepidermal eosinophil abscesses. In the benign form, in addition to the acantholytic degenerative epithelial changes there is considerable inflammatory infiltration leading to the formation of suprabasal pustules. Older lesions show the same changes as are seen in the malignant type

Pemphigus vegetans was first described by Neumann (VirtJhrfD 13 157 1886) See Hamberger and Rubel (BullJHH 14 63, 1903) Hartsell (JCutD 28 111 1910); Barker and Carter (BullJHH 30 162, 1919), Bloch (SchweizMWchn 41 116 1921) Schorer (MedKlin 17 720 1921) Kottmeier (ActaD-V 16 439 1935)

Etiology—The cause of pemphigus is unknown. Welsh (ADS 30 611 1934 JID 7 7 1946, 11 10 1948) isolated and studied a streptococcus, the intracutaneous inoculation of which produces bullae, but Curtis and Topp (JID 9 151 1947) could not confirm these observations.

Blood serum of a patient with pemphigus inhibits the growth of seedlings of *Lupinus albus Hartwegi* more than normal serum does (Macht: ADS 36 1022 1937) The phenomenon was utilized in designing a diagnostic test by Pels and Macht (ADS 23 601 1931) The Pels-Macht test enjoyed a considerable vogue but Hollander and Greb (ADS 34 650 1936) were among the first to point to the difficulty in obtaining reliable, consistent results.

Specific phytotoxicity of pemphigus serum is significantly reduced if the serum is exposed to x radiation, but serums from other dermatoses are not so detoxified and deep x ray therapy over the liver and spleen was followed in 10 cases by clinical improvement attributable to detoxification of the blood, reported Macht and Ostro (UCutRev 51 661 1947) Grace (ADS 29 885 1934) could find no substance toxic to rabbits in the serum of patients with pemphigus. The test is impractical thought Sansome and Forman (BJD 51 63 1939)

A virus has been reported in both pemphigus and dermatitis herpetiformis, obtainabl from the blood or blister fluid, which, inoculated into the eye of a rabbit results in paralysis convul ons, cachexia and death, by Urbach and Wolfram (ActaD-V 15: 129, 1934; ADS 33 83 1936; KlinWchn 15: 1479 1936) Wolfram (AfDuS 178: 240, 1939) and Werth (AfDuS 176 352 1938) Thi virus was transmissible from animal to animal and immunologic tests showed specific antibodies to it. I am sufficie tly convinced of the distinction between pemphigus and Duhring's disease, long confused on the Continent to be skeptical of such id ntity Fleck and Goldschlag (BJD 51: 70 1939) could not duplicate the result of Urba h. Vesicle fluid found pro ocative of vira e cephalitis, rarely transmissible in some rabb ts (Dostrovsky et al.: BJD 50: 41, 1938) perhaps owes it irritant property to the eosinophil c leukocytes within it as suggested by the studies of McNaught (J 111 1280 1938) of the Gordon test for Hodgkin's disease Balls fluid injected into animals subcutaneously by Werth caused no response injected intraocularly the foreign matter caused destruction of the eye and chick embryos were susceptible



Fig. 1249.—Pemphigus erythematodes. (Dr O. G. Costa.)
Fig. 1250.—Pemphigus vegetans. (Dr W Herbert Brown.)



Fig. 1251.—Pemphigus vegetans. (Dr D. E. H. Cleveland.)



Fig. 1252.—Pemphigus vegetans. (Dr W Herbert Brown.)

to the infection. Grace and Suskind (PSExperBiol 37: 1-4, 1937; JID 2: 1 1939) transmitted through mice a nonbacterial agent isolated from vesical fluid from 4 patients. The presence of a virus does not imply its pathogenicity Much remains to be done before the hypothesis of virus etiology of pemphigus may be considered proved, stated Markham and Engman (ADS 41 78 1940) No virus was found by Angulo (ADS 69 472, 1954).

Anemia is progressive the white blood cell count variable the sedimentation rate high and sodium chloride calcium and protein of the blood serum are diminished in proportion to the severity and extent of cutaneous involvement (Eller and Kest ADS 44 337 1941 Lever and Talbott NEngJM 231 44 1944) Such changes, accompanied by increase in the plasma volume, suggested those of adrenal cortical insufficiency and the possibility of benefit from the administration of adrenal cortical extract and sodium chloride. Indeed, remissions were obtained in a number of patients so treated by Talbott and Coombs (ADS 41 359 1940) Talbott et al. (JID 3 31 1940) and Goldzieher (ADS 53 42 1946)

The membrane of the red blood cells apparently is permeable to sodium and less so to potassium, for the sodium content of the red cells increased during exacerbations while the potassium conte t was relatively unchanged (Kurnick et al.: JID 4 481, 1941)

Laboratory studies by Fisher (ADS 66 49 1952) showed anemia, hyperplastic bone marrow no consequential alterations of liver function, increased urinary coproporphyria excretion, no consistent change in blood sodium or potassium, wide ranges of blood chloride concentration (never, however dangerously low) depression of serum albumin, increase of serum globulin, abnormalities of serum protein if the disease proved progressive, return of serum protein toward normal if the patient improved. Electrophoretic studies of serum proteins were performed by Lever (JID 14: 305 1950) who fou d the albumin *sometimes markedly diminished, probably because of loss through* denudation of the skin, while globulins were generally increased and regenerated well on high protein diet when the albumin failed to respond. Chemical studies of blood proteins were further investigated by Lever et al. (JID 19 65 195_) but the findings were not revealing

Pathology—In the early lesions, Kogoj (DWchn 102 287 1936) found intracellular edema intraepithelial vesiculation and the migration of polymorphonuclear leukocytes into the epidermis from the superficial cellular infiltrate in the dermis. In fully developed lesions, the papillae are swollen and edematous, with dilation of the intrapapillary vessels and more or less perivascular exudation. The bullous cavities lie just beneath the stratum corneum from which they may be separated by a few loosely adherent prickle cells. In the papillomatous lesions of pemphigus vegetans, the principal *changes are to be found in the upper dermis.* Both blood and lymph vessels are greatly enlarged and surrounded by pronounced cellular infiltration. The papillae are enormously hypertrophied, and there is a variable degree of acanthosis.

In post mortem studies of ? cases, Kraus (ADS 10 4-4 1924) failed to find the peculiar bodies n the spinal cord which were described by Corey (ADS 9 305, 1924) in fact no spinal cord changes of any kind were discernible (see Bald and Foldiri: AnndeD 7 626 1952) Adrenal lesions were found only in the patients who had received serumin, in necropsies studied by Humphreys and Donaldson (AmJPath 17: 767 1941) Fatty degeneration and passive congest on of the liver were abnormalities common to 9 necropsies reported by Gelli and Glass (ADS 44: 321 1941) In 4 necropsies reported by Kuhn and Iravas (ADS 57 801 1948) major lesions were found in the skin and mucosae, and visceral lesions were secondary with focal lesions of the liver kidneys, adrenals and gonads. The adrenal changes did not seem to be primary Necrosis of the arterioles was found in both primary and secondary lesions.

Histologic Criteria for distinguishing pemphigus from dermatitis herpetiformis were studied by Lapiere et al. (ArchbelgD 2 81, 1946 abs BJD 60 74 1948) In pemphigus the primary lesion is a cellular one affecting the basal Malpighian and, especially the granular layers, resulting in progressive alteration, up to and including necrosis so that prickles disappear and fissures form In this stage the dermis is neither edematous nor infiltrated. When dermal changes appear then the fissure swells out to form the bulla, and, at the acute angle joining its wall and floor some diseased cells float out into the cavity

In dermatitis herpetiformis, changes in the dermis appear to be primary the epidermal lesion starts with edema manifested by widened intercellular spaces, especially in the lower layers. The result is separation of epidermis from dermis or an intraepidermal bulla with rupture of the intercellular bridges. The epidermal cells are not altered other than mechanically they are to be found within the cavity the margin of the bulla is concave and dermal infiltration is conspicuous.



Fig 1253.—Pemphigus bleb. Compare Fig 54, p 81 (Dr Fred Weidman)





Fig. 1254—Pemphigus foliaceus, showing superficial character of dermatitis
Fig. 1255—Milia following healing of pemphigus lesions

Identification of pemphigus by cytodiagnosis can therefore be accomplished, it was shown by Tzanck (BsocfrançD 57 08 1947; AnndeD 8: 205 1948) for Giemsa staining of vesicle fluid shows, in pemphigus, Malpighian cells liberated by acantholysis, while the blister fluid in dermatitis herpetiformis contains no tissue cells, although blood cells may be present. In *scrapings* from the floor of the fresh bulla one can identify epidermal cells showing the degenerative changes of pemphigus, while such cells are not found in either

dermatitis herpetiformis or erythema multiforme reported Rook and Whimster (BJD 61 223 1949 62 443 1950) in confirmation of Tzanck s diagnostic method.

The characteristic changes in the epithelial cells of pemphigus are their detachment or loose attachment (acantholysi) their small size and rounded shape the large size of the nucleus in relation to the cytoplasm, the good preservation of the nuclei, and a condensed basophilic zone at the periphery of the cytoplasm (Blank and Burgoon JID 18: 13, 1952)

Tzanck cells are altered epithelial cells, rounded and devoid of intercellular attachments, enlarged and spherical, the periphery intensely basophilic so as to form a halo, the nucleus spheric and enlarged, the nucleoli prominent (Brennan: ADS 63: 451, 1953). Desmorhexis, by contrast with acantholysis, Bre nan used to designate the rupture of intercellular bridges by mechanical forces productive of bullae in dermatitis herpetiformis, erythema multiforme epidermolysis bullosa and bullous lichen planus.

Acantholysis is depicted in Fig 54 p. 51.

Subepidermal bullae do occur in pemphigus vulgaris sometimes, according to Hellier (BJD 66 49 1954)

Prognosis must be guarded. The patient s condition can nowadays usually be benefited Almost all victims eventually die of the disease it has been thought (Lever and Talbott ADS 46 348 1942) Treatment (q v) profoundly influences the outlook. The severity of the disease is variable and some patients in the days before cortisone and ACTH did recover I have believed that tense rather than flaccid bullae were favorable in prognosis and that oral and mucosal involvement were unfavorable.

The relation of pemphigus with pregnancy was reviewed by Samitz et al. (ADS 67 10 1953) in their case the fetus was unharmed

The blood picture shows terminal leukocytosis, the proportion of immature polymorphs being a sensitive index of change in the general condition ((Grace ADS 55 772, 1947 JID 8 339 1947) Eosinophilia diminishes with deterioration. Relative monocytosis is found in the terminal stage

Treatment.—The patient with pemphigus requires the most careful study and supervision. Hospitalization for long periods of time are highly desirable yet the expense of hospital and medicines is usually a serious problem. The patient suffers mentally as well as physically and requires and benefits from conscientious attention to morale. In the days before cortisone and ACTH, a physician dreaded the task of attending a case of pemphigus, for he usually watched his patient go downhill to a miserable death in spite of his most earnest effort

Cortisone and ACTH have revolutionized the treatment as well as the prognosis of the disease Their therapeutic effect has been far more impressive than any we have observed from other forms of treatment, wrote Cannon et al. (J 145 201 1951) in reporting 7 cases with great improvement of 5 patients and 2 deaths yet, there is little evidence that these hormones have influenced the basic causative factor in this disease. In acute cases, ACTH may produce benefit within 24 hours, rendering the patient nontoxic within a week (Aquilina et al. ADS 67 166 1953)

Cortisone is given by mouth in a dose of 3 or 4 of the 25-milligram tablets per day each dose accompanied by an enteric coated 5 grain potassium chloride tablet One may give more ACTH may help greatly when cortisone appears relatively inert and vice versa. The gel given intramuscularly once a day in a dose of from 40 to 80 units is likely to be sufficient. One must avoid giving ACTH over a long period of time while cortisone may be given in suitable dosage for years, I have observed, without producing ill effect. Records of the patient s weight are helpful in detecting waterlogging caused by these drugs. The results with cortisone and ACTH used in 28 cases were reviewed by Nelson and Brodey (AD 72 495 1955) The dose must at first be large enough to stop the appearance of new lesions. The maintenance dose is likely to be considerably smaller but it must be sufficient. Once controlled, the patient tends to remain controllable, although cases of pemphigus erythema

todes are sometimes hard to control. Complications seen by Nelson included thromboembolic phenomena, osteoporosis with fractures of vertebrae exacerbations of peptic ulcer and psychiatric phenomena of irritability for the relief of which Thorazine proved effectual.

A patient steadily improving may be given smaller doses than those which induced the remission, increasing the dose if he relapses. The use of ACTH and cortisone in no way diminishes the necessity for doing all the other things that may be beneficial They enable transfusions to be given without disaster in the initial period of treatment when transfusions may be imperative and they enable the patient to undergo minor surgical procedures for eliminating focal infection, upon which I am insistent.

Some patients with severe disease are kept from dying but not from suffering with extensive and miserable dermatitis. These are the problem cases for which at present one knows no solution.

It is my guiding principle to handle these cases with the utmost gentleness flares may follow intramuscular injections, flares may be expected after transfusions, and the elimination of focal infection may incite severe exacerbation. The patient is likely to suffer severely if any kind of foreign protein is introduced into him Since this is what any focus of infection does more or less continuously foci must be sought out and removed but one chooses a favorable time for doing the work, and expects at least a temporary setback to follow preventable, perhaps, by cortisone.

Locally, one must avoid friction, for the epidermis separates off with great ease. A bed patient may be taught to reduce the sandpapering effect of sheets, and good nursing care will aid in avoiding irritation. Liberal dusting with a bland powder is advisable using enough of it so that the patient, crusted as he may be does not stick to the clothes. Secondary infection must be combated meticulous débridement, Vioform Cream tetracycline by mouth in modest doses, tetracycline ointment, perhaps, and medicated baths are among the useful measures. Aqueous methylene blue yields flexible crusts, which gentian violet does not, and is sometimes helpful in spite of its appearance.

One may withdraw fluid from the blebs and inject into them 1% aqueous methylene blue. A mouthwash containing benzocaine 5 to 10% and oil of wintergreen, 0.3% in emulsion of almonds, 90 parts, and mucilage of acacia 10 parts, allays pain (Pillsbury et al. Manual of Dermat., Saunders, 1942) Therapeutic baths, sometimes the continuous bath, are useful I have occasionally been pleased by 1 15 000 mercuric chloride in isotonic saline. Bichloride of mercury possesses some virtue, for Sonnenberg (AnndeD 10 771 1939) reported 7 survivals out of 12 patients who were given 1 0 cc of the 1% solution intramuscularly each week. Pressure bandages as for extensive burns may simplify the nursing problem (Riley: ADS 54 711 1946) Penicillin merely controls, or aids in the control of secondary infection (O'Leary: ADS 50 430 1944 McLoughlin and Dobes SouthMJ 38 681 1945) Tetracycline is usually to be preferred for this purpose

Of internal medicines formerly used, arsenic in the form of acetarsone appeared to offer the most, empirically Oppenheim and Cohen (ADS 47: 40 1943) prescribed the 0.25 Gm. tablets to be taken before breakfast at the rate of 2 tablets the first day 3 the second, and 3 the third, followed by a rest of 3 days, then a repetition of the course. This was carried on until the patient had received a total approximating 1 tablet per kg. of body weight, or 70 tablets. A patient of Goeckerman (ADS 55 691 1947) received over a period of time 225 Gm. of acetarsone without ill effect Carbarsone in place of acetarsone and in similar doses was recommended by Little (ADS 52 397 1945) Carbarsone 0.25 to 1 Gm. before breakfast daily (PABA neutralizes toxicity) Amigen by mouth in adequate amounts, débridement petrolatum gauze and bland topical antiseptics were the measures used with good success by Combes et al. (ADS 57 532, 1948) Wise and Sulzberger (YBD 1934 p. 398) thought sodium arsenate of value; they gave the 2% aqueous solution intramuscularly daily in doses ascending to tolerance. They considered Germanin (see JChemTher 10: 106 1934; Dougers DWehs 102: 777 1936; Tomlinson and Cameron: ADS 38: 655, 1938) dangerous and disappointing although it has helped some cases.

Foreign protein therapy in 2 cases I saw immediately precipitated terminal exacerbation. Caro (ADS 37: 196, 1938) reported improvement in * cases when sulfanilamide was given. Vitamin D from 100,000 to 300,000 units per day has proved beneficial in the

hands of King and Hamilton (ADS 39 515, 1939) confirming Lodr and DeValin (UCalRev 36: 817 1932); and Tauber and Clarke (ADS 40: 82, 1939) also reported benefit with massive doses of vitamin D Lever and Talbott (ADS 43 341 1941) used dihydrotachysterol to increase blood calcium and argued that toxic manifestations of drowsiness, nitrogen retention, and kidney damage are reversible if recognized.

In supportive treatment, salt must be replaced, transfusions may be required, and vitamins are usually prescribed. Riboflavin appeared extremely helpful in a patient of Topping and Knoefel (J 114 2102, 1940) Grace and Hellman (ADS 53 249 1946) gave blood from patients who they said had recovered from the disease. The diet should be high in protein, but the salt free diet tried by a number of authors, including Keining (DWchn 97 1423, 1933) has, in my opinion nothing to commend it.

See Fiala (ADS 30 704, 1934) acute pemphigus developing during agranulocytosis Greenbaum (MRec 139: 283, 1934), intravenous Mercurochrome Cormia (ADS 32: 196, 1935), erythrol tetranitrate relieved pruritus Levin et al. (ADS 34 635, 1936), acute malignant case Prakken (ActaD-V 17 103, 1936) chloride loss Proppe (DMtschr 73 155, 1936), etiology Bade (DWchn 104 289 1937) liver extract beneficial, Kinnear (BJD 50 221, 1938) 7 cases, 2 in children Ebert and Omens (ADS 39 376, 1939) Mercurochrome failed Fox (ADS 50 140, 1944) Oppenheim treatment helped 2 cases Aleix (Lbe J 140 1203, 1949) rutin beneficial Greenbaum and Katz (ADS 61 158, 1950) x-ray therapy over spleen Lever and MacLean (JID 15 215, 1950) human serum albumin valueless Michalides and Reich (ADS 64: 326, 1951), 64 642, 1951) Stryker frame in physical management, Magner et al (ADS 64: 326, 1951) heparin helped Bettley and Fairburn (BMJ 2 326, 1951) Aureomycin and Chloromycetin Honduras t (ADS 60 394 195) inactivated autoserum therapy Conrad et al. (ADS 69 66, 1954), prolonged palliation expected with cortisone by mouth, but patient needs to be followed for an indefinite period of time Touraine (AnnD D 81 121 1954) classification of bullous diseases Hauser (DWchn 129 418, 1954) L.E. cells present and Tzanck cells absent in 2 cases of Senear Usher syndrome.



Figs 1256 and 1257—Brazilian "wildfire" pemphigus (Dr Oswaldo G. Costa.)

Fogo Salvagem Brazilian Wildfire Pemphigus.—This epidemic and fatal disease reported from Sao Paulo resembles acute pemphigus foliaceus (Brown ADS 69 580 1954) It affects patients of all ages, commencing generally with bullae on the face and thorax and becoming generalized Fever is present, high in the acute cases, and the patient complains of pain and sensations of heat and chills. Alopecia occurs, but hair returns if recovery takes place. Dystrophies result from interference with development, and gonadal defects impotence and bone changes have been called to the attention of North American dermatologists by Vieira (ADS 41 808 1940 abs J 119:

1230 1942; see J 121: 276 1943 130 893 1946) Costa (BJD 60 359 1948) described the disease as beginning with bullae and becoming universal with pustules crusts and exfoliation. Nikolsky's sign was present, but mucosae were not attacked. Marital couples and family groups have suffered in geographic foci, suggesting infectiousness. The disease might persist for from 2 weeks to a year and only 10% of those affected recovered. A description sent me by Costa enabled me to imagine of a disease I never saw that the features suggest the lichenoid dermatitis of nutritional deficiency complicated by infectious eczematoid dermatitis. Good nutrition, nursing care, and palliative medication topically have been recommended. Quinine has been thought helpful, but Atabrine was considered to be better though not curative by Fonzari (J 131 1092 1946)

OCULAR PEMPHIGUS

Ocular pemphigus is a tedious, eventually disastrous and fortunately rare disease affecting especially the mucosae, in which the chronic nonfatal course is characterized by bulla formation shriveling and adhesive scarring Scarring is extremely unusual in ordinary pemphigus, while in ocular pemphigus the skin is relatively little affected although some cutaneous scarring may occur (Lever and Talbott ADS 46: 354 1942; Lever AmJOphth 49 113 1944) Three stages respectively characterized by vesiculation, scarring and complication were separated by Rycroft (BritJOphth 18 571 1934) who found the acute cases fell in the 24-35 year age group the chronic ones in the 40-70 year group The onset with conjunctivitis might simulate trachoma tuberculosis, burns xerosis, syphilis or tarsitis.

Years may pass without interference with the general health but the adherence of cicatricial bands joining conjunctivae and globe bilaterally is typical causing narrowing of the palpebral fissures, ankylosis of the globes and eventually blindness (Klauder and Cowan AmJOphth 25 643 1942 ADS 49 362, 1944) Nasal, oral, pharyngeal, and even esophageal mucosae also support recurrent and painful bulla formation with resultant distress and deformity The prepuce adhered to the glans in the patient of Kanee (ADS 55 37 1947) The conjunctivae are seldom affected before other mucosae are. The skin lesions which may accompany those of mucous membranes include scaly plaques of erythema which heal with scarring and about which occasional bullae may appear They are located usually on the face or scalp and simulate those of pemphigus erythematodes. The bullae of ocular pemphigus are subepidermal.

Ocular pemphigus never undergoes transition into pemphigus vulgaris, according to Church and Sneddon (BJD 65 235 1953) whose essay included illustrations in color Yet the serums of these patients give positive phytopharmacologic reactions as in pemphigus, Macht (1951) told me.

In treatment, operative interference does not succeed Cortisone by mouth and by topical application gives considerable palliation, in my experience.

See Weber (ProcRoySocM 17 87 1923) oral and laryngeal lesions Fox (Larynx 36 676, 1926) lesions limited to mouth; Klauder (ADS 38 [illegible], 1938) 3 cases of "essential shriveling of the conjunctivae"; Halloran (ADS 46 246, 1942) 3 cases; Gallardo and Hardy (AmJOphth 26 342, 1943) [illegible] resembling vaccinia found in pemphigoid keratoconjunctivitis Wen [illegible] and Greetham (AmJOphth 29 1436, 1946) 2 cases; Selby and Parisi (AOphth 43 [illegible], 1950) case with onychoptosis.

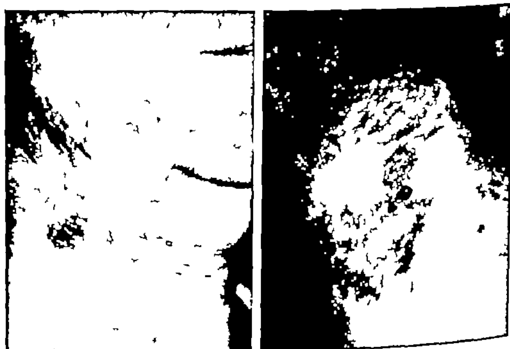
FAMILIAL BENIGN CHRONIC PEMPHIGUS

A familial dermatosis of benign and chronic course was described by Hailey and Hailey (ADS 39 679 1939 SouthMJ 83: 477, 1940) in which the individual lesions began as small vesicles which rapidly became flaccid bullae Early rupture followed, with formation of an amber-colored crust. The peripheral spread was bullous. Nikolsky's sign was present. The first report described serpiginous, impetiginoid lesions affecting the necks of

brothers, and 9 more cases were discovered in 4 generations of this family Ayers and Anderson (ADS 40 402 1939) independently described the same disease as recurrent herpetiform dermatitis repens. Lesions appeared in



Figs. 1258 and 1259 —Familial benign chronic pemphigus, respectively the first and second cases of disease, affecting brothers, reported by Howard Hailey (ADS 39: 679, 1939)



Figs. 1260 and 1261 —Familial benign chronic pemphigus, lesions on neck. (Franks and Traub ADS 43 657 1941.)

attacks, *arising spontaneously involving* the back and sides of the neck, axillae and genitocrural and perianal regions. They persisted for weeks or months rebellious to topical applications, sometimes healing under fractional doses of x ray therapy The individual lesions early in an attack were dis-

tinctly herpetiform and later consisted of a peripherally spreading raw slightly crusted or oozing area, with an undermined epithelial border and often a tendency to spontaneous healing at other portions of the patch.

The disease is familial it is benign it is chronic and the lesions make their appearance resemble and behave like the lesions of true pemphigus, wrote Hailey (SouthMJ 46 763 1953) The cause is not known. It usually first appears in young adults. The primary lesions begin as vesicles and



Figs. 1262 and 1263.—Familial benign chronic pemphigus. Fig. 1262 shows an intra epithelial vesicle, and Fig 1263 show acantholysis preceding bleb formation. (Dr Howard Hailey)



Fig. 1264 —Disruption of epidermis and crust formation, with only superficial inflammation, in familial benign pemphigus (Franks and Traub: ADS 43 667 1941.)

bullae They spread rapidly and rupture early and impetiginoid crust formation follows. Burning or itching may occur In the course of several days to several weeks the lesions heal. There is no subsequent scarring or atrophy Temporary increase or decrease of pigmentation may follow healing The size of the lesions or patches of lesions and appropriate symptomatic treatment materially influence the duration of the attacks. Adhesive and ultraviolet light frequently cause rapid spreading Friction, perspiration

and heat definitely influence the attacks as to frequency and duration, as well as add to the discomfort of the patient. The disease has been known to attack the eye.

Histologically one finds dyskeratotic splitting off of the epidermis, remarkably similar to that which occurs in Darier s disease, such that Becker and Obermayer (ADS 41: 11 0 1940) for example would name the condition Dyskeratosis bullosa hereditaria, while Goodman and Pels (ADS 44: 359 1941) entitled their essay Bullous dyskeratosis of the keratosis follicularis (Darier) type. ' Budding of epidermal ridges and acantholysis lead to the formation of intraepidermal clefts and vesicles, and cutaneous changes seem secondary to the epithelial changes wrote Pinkus and Epstein (ADS 53: 119 1946)

The pathologic changes, according to Hailey (1953) are essentially edematous, the two outstanding features being intraepidermal vesicles and a single layer of basal cells attached to the dermis. Separation of the epidermal layers, due to edema, produces irregular spaces or fissures like those of a dry mud bank. Cellular exudation is present in the lacunae, the prickle cells are edematous, and lymphocytes infiltrate the dermis.

While bacteria of possible pathogenicity have been cultured from the lesions, they are doubtless secondary They may cause pain and regional lymphadenopathy

After extensive study and review Ellis (ADS 61: 715 1950) attempted to classify Hailey and Hailey s disease as a vesicular variant of Darier s disease, and a patient in whom both diseases seemed to be present was reported by Finnerud and Szymanski (ADS 61 75 1950) The discussion of these essays is interesting, Hailey himself pointing out the differences which appear convincing to me and Caro commenting on the obvious clinical distinction of the two conditions.

In treatment zinc stearate generously applied and the avoidance of friction are to be recommended. Fractional x ray therapy is useful. Vitamin A in large dosage is sometimes quite helpful (Fraser ADS 46 326 1942) Treatment is basically palliative at present Hydrocortisone ointment seemed to benefit one patient, Hailey (1953) told me.

See Greenbaum (ADS 41 10 3, 1940) father and son, woman and sister, husband and wife , Franks and Traub (ADS 43 657 1941), 3 cases Franks and Rein (ADS 45 128, 1942), histologic resemblance to Darier' disease Carpenter (ADS 58 80, 1948), recurrences in 2 cases provoked by trauma and hot weather Balter (AnndeD 8 244, 1948) review and histology; Popper (ADS 58, 392, 1948) distincti features, Gougerot (AnndeD 10: 361, 1950) claimed priority for his 1933 observations; Coles et al. (BJD 62: 368 ff, 1950), cases; Salzberg (ADS 62: 568, 1950) Aureomycin palliative; Haber and Russell (BJD 62: 463, 1950) sisters; Koon (abs YBD 1951, p. 260) case, Warin and Wolff (BJD 63 63, 1951) recurrent herpetiform dermatitis repens; Wine and Leeb (ADS 67 77 1953) histology, corps ronds and grain cells in smears, a "delayed epidermal nevus"; Wehnert (ActaD-V 33: 211 1953) 7 cases, 3 helped with cortisone.

SCLEROTIC DERMATOSES OF UNDETERMINED CAUSE

COLLOID DEGENERATION OF THE SKIN

Colloid Degeneration (Hyaloma, Colloid Milium) a chronic and rather rare affection is characterized by the occurrence of pinhead to split pea size rounded, yellowish, pellucid nodules. The lesions develop gradually and occur as a rule, on the forehead, nose and cheeks. The nodules are discrete, circumscribed, waxy pale orange-yellow in color and of firm consistency They exhibit a tendency to grouping but they never coalesce. They superficially resemble vesicles, but when they are incised, only a small amount of gelatinous substance can be squeezed out. They give rise to no subjective symptoms but are persistent

Juvenile and adult forms were distinguished by Percival and Duthie (BJD 60 330 1948) and differentiation was made from senile elastosis with colloid change and from other dermatoses with colloid degenerations.

Etiology and Pathology.—The cause is not known. The majority of the reported cases have occurred in adults. The sexes are about equally affected. Long-continued exposure to the weather may be a factor Neither the sebaceous nor coil glands are directly involved. Labadie (ADS 16 156 1927) thought colloid degeneration best classified under the simple degenerations. Differential stains were used by Jager (ADS 12 690 1925) in a careful study of the pathology of the condition. He found cystlike areas, sharply demarcated, consisting of homogeneous, acidophilic material, masses of which were between hair follicles and separated from the epidermis by a slender band of connective tissue. In most sections colloid was divided into irregular segments, with cells along the lines of division suggestive of remnants of blood or lymph vessels. Other cells with relatively large, oval nuclei and cytoplasm containing vacuole-like bodies were also found in a few sections, representing surviving endothelial cells of otherwise destroyed blood and lymph



Fig. 1765.—Colloid milium. (Dr Joseph Earle Moore.)



Fig. 1766.—Colloid degeneration of the skin, showing dermal changes. (Dr John H. Lamb.)





Fig. 1767.—Early colloid nodules forming at the tips of papillae. (×150.) Section passes through side of the tips of two distended papillae and gives false impression that colloid has developed within the epidermis. (Percival and Duthie BJD 60 399 1948.)

Fig. 1768.—A large colloid nodule. (×50.) Homogeneous character of colloid material is evident in this alcohol-fixed specimen, and it did not take up the Congo red stain. (Drs. G. H. Percival and D. A. Duthie.)

vessels. The elastic fibers were swollen and broken into short segments, but not greatly diminished in number. Relatively large masses of collacin (Unna) were found, especially in the smaller and incompletely developed lesions. Degeneration of the connective tissue sheaths of the hair follicles was present. Chemically Jager found the colloid-like material to be insoluble in water, acetic acid, and alcohol. Testing for pseudomucin, it was boiled in 2% hydrochloric acid and neutralized, but it did not reduce Benedict's solution. Tests for amyloid were negative.

The colloid globules appear first at the tips of papillae in close relation to the sides of the capillaries and between the fine fibers of collagen, according to Percival and Duthie. Expanding upward and laterally the nodule slowly increases but is separated from the epidermis by a thin shell of compressed collagen. Superficial capillaries are dilated, and sparse histiocytic infiltration destroys some of the fine elastic fibers. The colloid may originate from serum proteins (Zoon et al.: BJD 67: 212, 1955).

Elastic tissue was absent from the masses of amorphous material in the pseudocysts of the dermis, which comprised the flat, shiny papules on the dorsa of the hands of the patient reported by Macleod et al. (BJD 44: 257 1932) but the blood vessels and accessory epidermal structures were unaffected. Similar cases were seen by Arguelles (abs YBD 1941, p. 46) and Stout et al. (AD 7 : 178 1955).

Diagnosis.—The disease is to be differentiated from milium, xanthoma, hydrocystoma, syringocystadenoma, adenoma sebaceum and benign cystic epithelioma. Resort must be had to a biopsy.

Treatment.—The nodules may be destroyed by curettage, the electric needle or by deep freezing with solid carbon dioxide. X ray treatment is unavailing. Vitamin C may help (Way and Hang ADS 44 1147 1941. Way ADS 45 1148 1942). Of 8 cases 3 healed spontaneously after a change of climate and the favorable influence of vitamin C was noted in some cases by Gilbert and Cox (MJAustral 2 21 1946).

See Wagner (ArchderHeilk 7 463, 1866). Besnier (AnndeD 10 461, 1879). Hartzell (JCutD 14 152, 1914). Highman (JCutD 37 148 1919). Ketron (BullJHH 29 145, 1918); Greenbaum (ADS 39 252, 1939) colloid degeneration in one. Andrews (ADS 41 744, 1940) case in 9-year-old girl. Reuter and Becker (ADS 46 695, 1943). Arnold (ADS 48: 262, 1943) case affecting hand, staining reactions of colloid resembled keratin; Schmidt (ADS 48 341, 1943), unilateral on neck of old man. Hand (ADS 49 224, 1944). Robinson and Tasker (ADS 52 139 1945) case cured by vitamin C. Hailey (ADS 54, 675 1946), 2 cases, vitamin C of questionable value. Ferreira Marques and Van Uden (AfDuS 182 1, 1940) histologic indications that changes involve elastica only. Arnold (ADS 48: 262, 1943) colloid pseudomilium. Stout et al. (AD 72 178, 1955).

PSEUDOXANTHOMA ELASTICUM

This rare affection is characterized by aggregations of flat yellowish, intracutaneous abnormality in minute circumscribed and diffuse plaques forming patches symmetrically located in the flexural folds, axillae, sides of the neck, upper and inner aspects of the thighs, and over the abdomen in extensive cases. While the affected skin may hang loose it is not hyperelastic (Wigley and Freudenthal BJD 56 136 1944). The lesions are asymptomatic but persistent. Angioid streaks of the retina occur in about 25% of the cases (Benedict and Montgomery AmJOphth 18 205 1935) the association of skin and retinal changes being known as the Gronblad-Strandberg syndrome (Urbach and Nekam KlinWchn 15 857 1936).

Histologic examination of an enucleated eye which had shown angioid streaks yielded no microscopic evidence of their explanation for Benedict (J 109 473 1937). Angioid streaks were ascribed to degenerative rupture of the elastic membrane of Bruch by Urbach and Wolfram (AfDuS 176 167 1937) in whose patient similar damage of the aortic elastica was also found at autopsy. Benedict and Wagener (AmJMedSci 205 301 1943). Hagedoorn (AOphth 21 774 935 1939) and others have confirmed such an explanation, but Ebert (ADS 48 75 1943) denied that satisfactory elucidation of the nature of the streaks had been achieved. The plaques consist of alteration in the middle and lower dermis only, where circumscribed regions contain clumps of swollen and degenerated elastic fibers and basophilic degeneration of the collagen. Giant cells and xanthoma cells are absent.

Calcification and even bone formation within the abnormal skin have been observed in rare cases (Beeson ADS 34 729 1936; Grönblad ActaD-V 28 270 1948). Calcium phosphate is richly present in the lesions, including those

not manifesting calcification clinically (Finnerud and Nomland ADS 35 653 1937) confirmed by Lobitz and Osterberg (JID 15 297 1950) Normal collagen fibers extend throughout the granular zone of degenerated tissue, Hannay (BJD 63 92, 1951) observed and, noting that true elastic fibers are sparse and that damaged collagen is favored as a site of calcium deposition he suggested that the hypertrophied tissue is altered collagen rather than elastica.



Fig. 1269—Pseudoxanthoma elasticum. (Dr D. D. H. Cleveland.)



Fig. 1270—Pseudoxanthoma elasticum, axillary involvement. (Dr O G. Costa.)
Fig. 1271—Pseudoxanthoma elasticum, ul[illegible] involvement. (Dr O. G. Costa.)
Fig. 1272—Histologic structure of pseudoxanthoma elasticum. (Dr Stuart C. Way)

Familial incidence sometimes occurs, as in the sisters reported by Shepard (ADS 42 680 1940)

Pseudoxanthoma elasticum is usually harmless, but it has nevertheless been found causative of scotoma, retinal hemorrhages and even blindness (Hubler ADS 50: 51 1944 Silvers and Wolfe ADS 45 1142, 1942) Revell and Carey (SouthMJ 41: 782, 1948) stressed the systemic aspects of this dystrophy of elastic tissue, the cutaneous manifestations of which are named pseudoxan-

thoma elasticum. Hypertension, irregularities of pulse calcification of peripheral vessels, and abnormal bleeding into the gut, uterus, bladder and brain have occurred, and the incidence of thyrotoxicosis and diabetes mellitus seems abnormally high in these patients. The systemic effects of widespread vascular elastic tissue abnormality were reviewed by Szymanski and Caro (AD 71 184, 1955) differentiating atherosclerosis aneurysm, dilation, calcium deposits, hypertension, hemorrhages which have been known to be fatal, osteitis deformans associated with angioid streaks, vascular damage to the central nervous system and various other visceral infirmities may result.



Fig. 1273.—Pseudoxanthoma elasticum stained to show degenerated elastic tissue, Weigert hematoxylin nerve tissue stain. (Throne and Goodman ADS 4 419 1921.)



Fig. 1274.—Angioid streaks of retina. (Dr Cecil O'Brien.)

The cause and cure of pseudoxanthoma elasticum are unknown. Elastase [illegible] elastolytic factor studied by Baló and Banga (SchweizZtsch PathBact 1 350 1949) dissolves elastin without liberating peptides or amino acids. Fibers appearing morphologically in section to be elastic tissue show variable susceptibility to the enzyme [illegible] suggesting that the fibers in pseudoxanthoma elasticum manifest increased resistance suggesting the disease represents an elastic fiber dystrophy (Findlay: BJD 66: 16, 1954)

See Clay and Hu d (SouthMJ 31 1 7 1938), case in Negro, showing in early stage disappearance of angioid streak on pressure Wiasecke (DWchr 10 1396, 1938) abnormal in ol ement, 2 cases. Ildek (Ztsch Augenh 9 1 1938) rupture of membrane of Bruch accounts for angioid streaks. Photinos (BullsocfrancD 46 1401, 1939) 2 cases from Greece, Lois and Est vas (ADS 45 383, 1942), case with disturbance of elastic fibers in angioid streaks. Griffith and Kl eder (ADS 47 441 1943), extremely extensive [illegible] (ADS 43 314, 1941) case apparently benefited by tocopherols, 300 mg daily orally

Elastoidosis, Nodular, Cutaneous, With Cysts and Comedones.—This unusual syndrome was reviewed and 8 cases recorded by Favre and Racouchot (AnndeD 78: 681, 1951). It is characterized by the presence of numerous small nodules, usually surmounted by comedones and disordered pilosebaceous elements resulting in cyst formation. The nodules are yellowish, somewhat translucent, and cystic, with dilated hair sacs and trophic sebaceous glands. Folds, wrinkles and furrows underlie the superficial changes. The region affected is generally the face, ears and back of the neck. The onset is insidious, and the patients have been of advanced age, 67 years on the average. The cause is unknown. Sections show the upper cutis to be abnormal with a thick, compact, structureless appearance due to the disappearance of elastic and connective fibers from the papillary region and about the vessels and nerves.

Akrokerato-Elastoidosis was the title given by Costa (Dermatologica 107: 164, 1953; ADS 70: 228, 1954) in describing a unique case. The patient was a young woman with a symmetrical, papular eruption of the hands and feet. The skin over the interphalangeal and metacarpophalangeal joints was thickened with coarse folds, and embedded in this were numerous small, pearl-like transparent papules. Sections showed increased spacing of the collagen fibers, but mucin was not demonstrable.

KNUCKLE PADS

Fibrous nodules occasionally develop in the deep cutis and subcutaneous tissue overlying the extensor surface of the proximal interphalangeal joints of one or, as a rule, several of the fingers. The nodular pads are of split pea to hazelnut size. They move over the bone beneath but adhere to the overlying skin. When the finger is extended, the lesion is soft and movable; when flexed it is hard and fixed. The skin surface is slightly hyperkeratotic. The

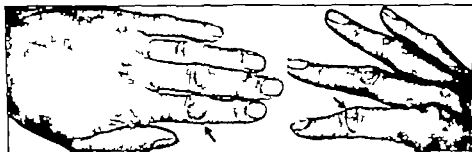


Fig. 1278.—Knuckle pads. (Dr. F. Ronchese.)

lesions have their onset singly as a rule in youth or later age, and may be somewhat painful during the few weeks or months of their development. Once developed they are permanent, being sometimes a source of discomfort or pain, and sometimes asymptomatic. They may appear one after another so as to cross the hands from one side to the opposite side. Rarely the distal interphalangeal joint is affected, and occasionally the toes, but the thumb has never been observed to be the site of a lesion. X-ray examination reveals no bony abnormality and the lesions are not cystic.

Garrod (StBarthHospRpts 29: 157, 1893) reported 12 cases, 5 of which affected women; he (BMJ 2: 8, 1904) extended his observations and noted especially the association in 6 of 12 examples of knuckle pads with Dupuytren's contracture of the palmar fascia. Jones (BMJ 1: 759, 1923) distinguished the lesions from those of gout and from arthritic osteophytes; Hale White (QuartJMed 1: 479, 1907) thought them purely fibrous. The description by Weber (BJD 50: 26, 1938) was called to my attention by Dr. F. Ronchese, whose photograph of a patient is herein reproduced. See also Moncorps (ZentralblHuG 54: 291, 1936) and Krantz (DWehn 197: 945, 1938).

Treatment that is effective is unknown to me. Hypotheses have been offered regarding etiologic factors such as habitual rubbing of the knuckles and avitaminosis A (p. 728).

See Moncorps (ZentralblHuG 54: 291, 1936), "cushion-like keratoses," quoted by Wise and Sulzberger (YDD 1937, p. 274), different from Vörner "helodermia"; Krantz (DWehn 107: 945, 1938): 2 cases and review, disorder identical with Milian "keratomes en nappes des mains";

Winer (ADS 40 1068 1939) histologic increase in deep dermal fibrous tissue, Weber (ADS 44 526, 1941) 2 cases Wise (ADS 49 144, 1944) case presentation, interesting discussion Strobel (AfDuS 187:91 1945) attributable to irritation and callosity review and bibliography Schultz (DMedWchn 74:328, 1949) 5 cases.

SCLERODERMA AND RELATED INDURATIVE *DERMATOSES*

Scleroderma is a chronic dermatosis characterized by boardlike hardening and immobility of the affected skin. The ivory-colored patches may be circumscribed or diffuse Swelling hypertrophy calcification perhaps, and eventual atrophy of the collagenous tissues are the features. Cases exemplifying the localized linear acrosclerotic and diffuse types were exhibited by Downing (ADS 58 655 1948) Visceral manifestations were reviewed by Beerman (AmJMedSci 216 458 1948)

Diffuse Scleroderma.—The initial manifestations may be those of edema, or the affected areas may present more or less evidence of fibrosis from the first. The majority of cases occur in adult life The affected skin is pinkish in color smooth and waxy and pits slightly on pressure. The patches may develop insidiously or rapidly and vary greatly in size and contour At the margins they gradually shade off into the sound skin. The sites of predilection are the limbs, face and upper half of the body The epidermis and its accessory structures undergo secondary atrophic changes. After the disease has existed for some time the skin becomes hard yellowish, ivorylike and firmly adherent to the underlying tissues. The face may become masklike and expressionless, and the hands assume a clawlike appearance sclerodactylia. Telangiectases are likely to develop on the lesions as well as at their margins, and pigmentation is common. Sensibility of the affected parts may be increased but generally is diminished. It is seldom entirely lost. Disturbances such as canities vitiligo Raynaud s phenomenon, sclerodactylia, and abnormal calcification are occasional accompaniments. Tension, ulceration and necrosis sometimes occur over the sites of the bony prominences the resulting lesions being extremely stubborn and resistant to treatment.

Scleroderma affects also subcutaneous and deeper tissues, producing interference with respiration and ankylosis of the joints, so that the patient becomes pitiably helpless. It may cause a characteristic form of pulmonary fibrosis (Murphy et al. J 116 499 1941) with cystic bronchiolar hyperplasia (Getzowa AI ath 40 99 1945) Esophageal involvement causes dysphagia with blocking of firmer foods sometimes necessitating gastrostomy (Weissenbach et al. BsocfrançD 44 1060 1937 Lindsay J 123 745 1943) Atony *diminution of peristalsis and stenosis are found on fluoroscopy* and frequent dilation with small sounds may be helpful (Olsen et al. AIntM 70 189 1945) Heart failure with peculiar myocardial scarring was reported by Weiss et al. (AIntM 71 749 1943)

O'Leary and Nomland (AmJMedSci 180: 95 1930) reviewed 48 examples of the general type and 55 of the local. They found no parallelism in onset, course appearance o prognosis for the 2 types despite the similarity of the skin changes. The general disease is a serious nd almost irremediable one, they found with a life expectancy of only 7 years, an association w th sclerodactylia in 90% of the cases, and a curability of only 6% Du ham (AIntM 4 467 1928) published an interesting st dy comparing scleroderma with cal i osis. Beale (SouthMJ 22: 895 1929) emphasized the necessity for careful investigat n of the autonomic nervous system. Brown et al. (AnnIntM 4: 531, 1930) concl ded that v somoto disturbance may antedate for years the onset of organic changes in the skin Hypersen tiveness to cold is expressed by a proclivity to attacks of pallor and cyanosis.

Following transplantat on of a patch of scleroderma by means of a pedicle flap, the lesion increased in ize (Comel Dermatologica 96: 366, 1948).

Creatinuria wa found n 6 cases and attributed to muscle atrophy by Epstein and Ayres (JLabClinM 23 607 1937)

Fibrous and c stl lung changes were present in 3 patients of Dostrovsky (AI[?] 53: 1 1947) Jackman (*Radiol 40 163, 1943*) *discussed roe tgenographic findings.* In[?]terrelationships with dermatomyositis (q.v.) were discussed by Dowling (*BJD 5*[?] 1940) and O'Leary (CanadMAJ 48: 410 1943)

The disease in children is generally scleredema rather than true scleroderma; the 3 children patients of Oliver (ADS 25: 72, 1932) whose symptoms followed infectious diseases and eventually disappeared, were of this type. A girl 6 years old, reported by Crawford (ADS 33: 506, 1936) presented acutely spreading morphea with atrophy in association with rheumatoid arthritis and ankylosis of the hip joints. An astounding



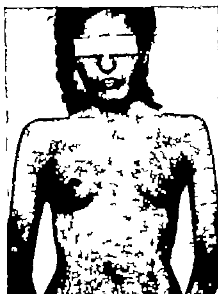




Fig. 1276.—Guttat morphea of 3 years' duration in a 14-year-old girl, distributed like a linear nevus (Dr Grover Wende)

Fig 1277—Generalized, advanced scleroderma. (Dr O. G. Costa.)

Fig. 1278.—Deep scleroderma, showing fibrous extensions about trophic muscle fibers (Dr Fred Weidman)

case of universal type was reported by Pashman (AmJDisChild 55 135 1938) Only 3 cases of true scleroderm in infants were acceptable to Dias and Woringer (BSocfrançD 36: 960, 1929)

Scleroderma-like changes may follow peripheral nerve injury (Halter: DWchr 109: 1139 1930)) see Glossy skin. Stiffness, dryness and a hidebound texture of the skin may

develop below the level of a transverse injury of the spinal cord (Kerr and Noble: Calif WM 45: 346, 1936).

Treatment.—Injections of a pituitary extract were helpful in several cases treated by Oliver and Lerman (ADS 34: 460, 1936). It is now known that



Fig. 1279.—Morphea becoming atrophic.



Fig. 1280.—Morphea.



Fig. 1281.—Scleroderma: degeneration of collagen and atrophy of epidermis.



Fig. 1282.—Biopsy from dorsum of hand in acrosclerosis of 5 years' duration. Note atrophy of hair follicles and sebaceous glands, homogenization of collagen and thickening of walls of blood vessels. (O'Leary and Waisman: ADS 47: 382, 1943.)

cortisone is the drug which produces benefit for sure, and improvement may be expected to appear promptly and is maintained by repeating the course of treatment if remission takes place during periods when the chemical is not

given (Kierland and Hines ADS 64 549 1951; Taubenhaus and Lev AIntM 87 583 1951 Sharnoff et al. J 145 1230 1951) Retreatment will yield the same degree of benefit that the first course of cortisone does. Visceral disabilities respond as well as the skin lesions do ACTH appears to be less effective One may recall that giving cortisone tends to decalcify while giving testosterone promotes calcification

Since calcium and phosphorus are retained in the body in scleroderma, and urinary excretion is small, large doses of viosterol may be given in order to prod ce ma ked in crease in uri ary calcium cretion. Thi seemed to help patient but did not cure them, noted Cornbleet and Struck (ADS 35: 188, 1937) Norman (Geriat 24, 1947) thought vitamin D the treatment of choice. Ingels (ADS 50: 72, 1944) obtained improvement with Padutin 10 units b.i.d. Vasodilation with sodium nitrite yielded be efit for Cipollaro (ADS 53 831 1946) Bernstein and Goldberger (ADS 50: 226 1944; J 130: 570, 1946) have had some success with dihydrotachysterol. Acid fast rods were found in the sputum blood and smears from the nose and subcutaneou tissues by W ertheim t al. (NJ mevMRJ 44: 256 1947) who we e struck by the similarity of scleroderma to leprosy and they thought Promin therapy beneficial. Gold injections were believed helpful by Preininger (DW bu 103: 853 1037) Bismuth by mouth was recommended by Stryk et al. (JID 11: 899 1949) Ammonium chloride w given in large dosage in an attempt t decalcify the skin by Wile and Curtis (ADS 58 744, 1948) A derivati e of cinchoninic acid yielded in 3 cases ben fits that were considered remarkable by Rennie et al. (BMJ 1: 393, 1951)

Vasodilation induced b io tophoresis of Mecholyl seemed benefi ial in the e perience of Darvee and Wright (AmHeartJ 14 603 1937) Iontophoresis with hy aluronidase appeared palliativ while it was being used by Popkin (JID 16: 97, 1951; Angiology 3: 335 1952) Procai e hydrochloride by intra enous inf sion produced rapid improvement, according to Turne and Shmidt (J 144: 1500 1950)

Despite the absence of laboratory evidence of protein depletion, a regimen of hyperproteinization was followed by gain of weight, softening of induration healing of ulcers, improvement in flexibility and a feeling of well being in 4 cases of Co Tui et al. (JID 15 181 1950) In 3 cases with pulmonary as well as cutaneous involvement cortisone therapy was subjectively and objectively temporarily helpful, the skin showing more improvement than the viscera (Salomon et al. AIntM 95 103 1955)

The patient should reside in a warm, equable climate. Physical therapy with baths and massage has value Sympathectomy (Evans et al. J 151: 891 1953) and parathyroidectomy are of questionable value. Parathyroidectomy was helpful in 13 cases curative in 2, according to Leriche et al. (Surg 1 6 1937) but the results of such surgery appeared temporary and inadequate to justify it stated Liuzzo (abs J 114 931 1940)

See Brady and Deilin (ADS 36 86, 1937), case with calcinosis, differentiation from dermatomyositis; Weissenbach et al. (AmmleD 3 81, 198, 1938), esophageal invol ement Kunsbold (DWchn 106 62 1939) hyperparathyroidism not alone t fault, etiology appears pluriglandular; Howles (NOrlM&SJ 92 6, 1939) Burch (ib, p 12) Ochsner and DeBakey (ib., p. 21) clinical, pathologic physiological, and surgical aspects; Raf ky and Herain (Gastroenterol 6: 36, 1946) esophageal symptoms Harvier and Bonduelle (PresseM 55 309 1947 young woman with calcification of liver and spleen Fox (ADS 55 389, 1947) case visceral in ol ement Lloyd and Tonkin (Thorax 3 241, 1948) 4 cases with pulmonary fibrosi ; Cil (Anal tM 34 862, 1951) visceral and endocrine disturbances Sev ile (JID 62 407 1951) case with nodules, electron micrographs of collagen changes H tchesson (VaMMonth 78 450 1951) isceral lesions Ormea (Hautarzt 3 301 1952), histologic abnormalities in sympathetic ganglia Helgelman et al. (NEngJM 249 45, 1953) systemic manifestations in 18 cases included Raynaud's syndrome in 12, cardiorespiratory embarrassment in 14 dysphagia in 8 nd bnormal EKG nd diffuse, fibrotic collagen disease in those undergoing necropsy; Kettel (Chirurg 24 121, 1954) 3 cases with systemic manifestations; Hagele and Pfister (KlinWchn 32 482, 1954) 6 cases, roentgen changes Korting (AfDuS 198 396, 1954) keloidal scleroderma; Kamarich et al. (DMedWchn 79 1603, 1954) prolonged sleep therapy Abrams et al. (AIntM 94: 61 1954), gut involvement, demonstration of dilation and diminished peristalsis; Fabre et al. (bs J 167: 1159 1958) heart involvement, left ventricular decompensation symptoms; Leinwand et al. (AnnIntM 41: 1003, 1954) 104 females 42 males age range 3 to 65 years, 4 deaths episodic course, 8 cases improved on cortisone Gonzalez (abs J 159 73, 1955) 75 Chilean cases.

Acrosclerosis as originally described by Sellei (AfDuS 163: 343 1931 170 464 1934 173 3 _ 1936) is a syndrome in which are combined features of both Raynaud's phenomenon and scleroderma As described by Hollander and Vogel (LaMJ 43 1089 1940) and by O'Leary and Waisman (ADS 47 382, 1943) the early symptoms appear to be due to intermittent arteriolar spasm of the upper extremities, and sclerosis appears contemporaneously or at some time even years, afterward. The lower extremities are involved less,

may even escape. Facial sclerosis develops with the sclerodactylia or later In fully developed cases the skin of the fingers and hands is smooth, shiny and tense and pale cyanotic or mottled in color *The terminal phalanges are* tapering or rounded, the integument here being rubbery or hard and bound fast to underlying structures. Proximally there is progressive decrease of induration which seldom extends above the elbow The hands and fingers are cool and moist and stiff and clumsy When the Negro is affected, pigmentary changes may in the early stages obfuscate the diagnosis, for spotty partial depigmentation is the conspicuous feature of the patient at first glance

The fingertips may develop scaling fissuring crusting or ulceration and scars, and calcareous deposits may be present in them. Facial skin becomes drawn and stretched, with smoothing of the lines of expression. It is not hard

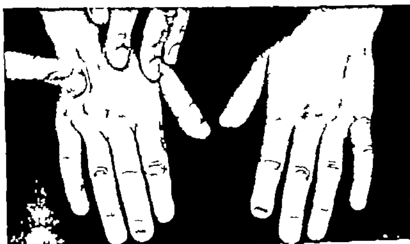


Fig 1283.—Acrosclerosis tense, smooth kin over fingers and hands, clubbing of nails, and shortening of terminal phalanges. (O'Leary and Waisman ADS 47 382, 1943.)



Figs. 1284 1286.—Early acrosclerosis, illustrating diminished mobility of features, puckering of lips and chin, nd inflexibility of skin. (Drs. O'Leary and Waisman)

but rather taut. Sclerosis fades over the neck and upper chest. Small telangiectatic macules are sometimes present. While the scalp may share the abnormality alopecia does not result. After the hands, forearms face and upper chest have become involved it is unusual for further extension to occur But the chest may become stiff and the vital capacity reduced, and the patient is considerably handicapped.

The abnormalities faded markedly over a period of years in some of O Leary and Waisman s patients, but did not entirely disappear These authorities regard sclerodactylia as a potential complication of Raynaud's syndrome and would combine scleroderma with Raynaud s phenomenon and Raynaud s phenomenon with sclerodactylia in the one title as Hutchinson, whom they quoted did in 1893

The esophagus is frequently affected, especially when the face and neck show the changes, and dysphagia results (Truelove and Whyte BMJ 2: 873 1951) An adenoma of the adrenal gland was found at autopsy in the patient of Barlow (ADS 39 1021 1939) Changes in the sympathetic nervous ganglia and fibers were demonstrated by Sunder Plassman (DeutZtschrfChir 251 125 1938) and attributed to toxic effects. He described edema and swelling of Schwann s sheaths, the axis cylinders and the finest blood vessel nerve plexuses.

Sclerodactylia like changes occurring in 39 of 178 cases of myocardial infarction seemed due to anoxia and reflex vasoconstriction (Johnson AnnIntM 19 433 1943)

The cause is unknown. Prognosis is more favorable than in diffuse scleroderma. If sclerosis has not extended beyond acral parts in 2 years, generalization is unlikely to take place subsequently

Cortisone by mouth is extremely gratifying in palliation. Since this drug became available surgical methods have become obsolete yet parathyroidectomy appeared to yield much benefit in 3 cases associated with Raynaud s symptoms, although the improvement was limited, reported Bernheim and Garlock (AnnSurg 101 1012 1935) Sympathectomy is especially suitable in relief of this acral type of scleroderma, according to Adson (J 106 360 1936)

See Brown et al (AnnIntM 4: 531 1930) Feldman (ADS 43 395, 1941) malignant case beginning with fibrosis of the lungs in Negress of 30; O'Leary (ADS 54: 633, 1948) 5 cases Curtis (ADS 61: 677 1900), use of PABA Littler and Canter (Lancet 1: 130 1951) review relation of adrenal abnormality

Circumscribed Scleroderma (Morphea) is characterized by the occurrence of one or more circumscribed, grayish sclerotic plaques, usually surrounded by delicate violaceous areolae. Occasionally the plaques are elongated and bandlike; rarely they are distributed in the manner of a linear nevus. The course of the lesions is variable. An early edematous erythematous stage may be prolonged for weeks or months. The plaques may disappear spontaneously leaving little or no trace or they may give rise to circumscribed atrophic areas which persist indefinitely

Bulla formation is sometimes seen (Templeton ADS 43 361 1941 Reich DWehn 121 486 505 1950) Calcification within the lesions has been noted, as in the patient of Treble (BJD 64 291 1952) When Thiersch grafts were interchanged between normal and abnormal sites, the pathologic tissue became normal in the abnormal environment, whereas the normal graft assumed the changes of the abnormal site into which it had been transplanted, reported Haxthausen (ActaD-V 27: 352 1947) The transformation did not proceed from the margin but appeared simultaneously in all portions of the grafts. The disease affecting a father and his daughter was reported by Rees and Bennett (ADS 68 360, 1953) Biochemical studies of the collagen ground substance using trypsin digestion, were reported by Musso (BJD 66 377 1954)

The lesion sometimes takes the form of a vertical, midline stripe on the forehead, en coup de sabre. Such cases sometimes affect the gums, too (Barber BJD 56 94 1944; Davis and Saunders ADS 54 133 1946) Chloroquin therapy seemed to help the young patient of Scully (ADS 70 676 1954) Compare hemiatrophy of the face.

Li ea scleroderma was intensively studied by Rubl (ADS 53: 1, 1948) who compared the distribution of the lesions with the segmental distribution of innervation. They do not follow the peripheral nerves but are usually distributed in the long axis of one or several spinal root zones. More than half of his 13 patients had lumbo-sacral spina bifida occulta. Fou of them h d lesions of morphea as well as of linea scleroderma, suggesting a common pathogenesis. Features ttributed to trophic alteration in central nervous system disease resemble features of scleroderma, R bi remarked.

TREATMENT —Histamine ointment (Imadyl) and x ray therapy in doses of 200 r with 1 mm al. filtration at intervals of 3 weeks are helpful in the early stages when infiltration exists. Stokes (ADS 53 65 1946) favored injections

of bismuth see Flood and Stokes (ADS 57 810 1948) Dennie and Morgan (SouthMJ 40 860 1947) reported success with fever therapy induced by hot baths, while giving cod liver oil Artane an antispasmodic drug appeared helpful in 8 cases of Robinson (JID 19 171 1952) It is doubtful if treatment really helps. The disease in most instances may safely be disregarded.

White-Spot Disease is a loose designation for any one of several different disorders which manifest small depigmented atrophic lesions, including atrophic morphea, atrophic lichen planus lichen sclerosus and macular atrophy (q.v. see *Wise and Shelmire ADS 18 179 1928 Ormsby ADS 40: 133 1939 Montgomery and Hill ADS 42 755 1940 Vidal abs BJD 63 38 1951)*

SCLEREDEMA

Piffard described the condition in his text in 1876 (Saffron ADS 47 110, 1943) although credit is usually given to Buschke (KlinWchn 39 955 1902) Scleredema is characterized by benign but spreading induration and swelling of the skin and subcutaneous tissues. The skin is smooth and its consistency much increased but it does not pit on pressure. Sensation is unaffected. There is no atrophy pigmentation, or hair loss, and there are no signs of inflammation. The changes often begin at the nape of the neck and spread over the face and trunk affecting the lower parts of the body generally to a lesser degree The condition usually follows some febrile disease cases being recorded of its succeeding fevers of undetermined etiology influenza, oral infection following extraction of a tooth, scarlet fever acute tonsillitis, erysipelas and even impetigo contagiosa The case of Frank (ADS 36 1052, 1937) succeeded tonsillitis and the tongue especially was involved. Sometimes a blotchy erythematous rash precedes the thickening of the skin. Pleural effusions, pericardial effusions and hydrarthroses are said occasionally to occur (Vallee NEngJM 235 207 1946)

Pathology—The chief histologic changes are in the collagenous bundles, which are swollen to several times their normal size; but the disease is noninflammatory Mucedematoid material has been described about the vessels and epidermal appendages as well as between the collagen fibers. The nature of the mucinous material is obscure observed Swettze and Lawmon (ADS 37 420, 1938) and there is no response to thyroid medication. Touraine et al. (AnndeD 8 61 193) described moderate lymphocyte and plasma cell infiltration along with hemic lymphocytosis. The muscles may be involved and so become flabby

Hypoproteinemia and hyperlipemia were found in an infant with scleredema and nephrosis following otitis media and mastoiditis, by Janet et al. (BullsocPédiat 33: 996, 1035), although ordinarily scleredema is not associated with nephritis (Fischinsky: MünchMWchn 84 1448, 1937)

Diagnosis.—Scleredema is different from scleroderma, despite the resemblances. Scleredema follows some acute infection. It involutes spontaneously without subsequent atrophy It does not progress, bind down cause contractures or result in death. The hands and feet are almost never affected but if so the involvement is only of the skin of the dorsum without ischemia of the digits. Pigmentary changes are absent in scleredema, calcification never occurs, and histologically the changes do not include sclerosis, calcification or endarteritis.

Treatment.—Scleredema is a self limited disease. Usually from 3 to 1? *months are required for its involution. Epstein* (J 99 890 1932) found massage and hot baths useful but endocrine therapy was without benefit O'Leary et al. (AmJMedSci 199 458, 1940) reviewed 15 cases and recommended artificial fever massage and elimination of focal infection It is possible that cortisone or ACTH would be of service but no report of the use of these agents in this disease has come to my attention.

See Freund (Ztblf[illegible]HuG 33 302, 1930) histology, Arnold (ADS 31 210 1935), in girl with tuberculous cervical lymphadenitis, Jastman ([illegible] YBD 1948, p. 462 following whooping cough, W[illegible] et al. (ADS 60 909 1949) case of [illegible] year duration [illegible] 51 Leiwand (AnnIM 34 226, 1951) autopsy and review of 103 cases reported since 1900

SCLEREMA

Sclerema Adiposum, unlike fat necrosis of the newborn (q v) which usually affects large and otherwise normal infants is seen chiefly in undernourished debilitated and premature infants. It was first accurately described by Underwood (Diseases of Children, London, 1784) It may appear suddenly on the third or fourth day, or at any time in the first weeks of life, without apparent cause except undernourishment and debility or at a later age in babies with gastrointestinal disorders, especially severe diarrhea that results in dehydration and gross malnutrition.

The lesions are seen first on the lower extremities, usually on the calves, and they extend upward rapidly to involve the entire body with the exception of the palms soles and scrotum, where fat is absent. The skin, instead of being apparently swollen and reddish as in fat necrosis, is shrunken, smooth and whitish or waxy in color It is puttylike and cold to the touch the temperature being nearly always markedly subnormal. Resembling fat necrosis, however the indurated tissues are notably hard and do not pit on pressure. In the severest cases the infants are unable to move and the pulse and respiration become increasingly slower a condition which Northrup (TransactAm PedSoc, 1889 p 140) likened to that of a half-thawed cadaver

The disease is fatal in the great majority of cases, the duration being only a few days as a rule Garrod (TrClinSocLond 30: 129 1897) reported resolution and recovery in one patient. ACTH cured 2 cases rapidly for Eisenoff et al (J 155 905 1954) it did not help the patient of Fauser (abs J 154 939 1954) but cortisone did.

The disease was aptly named cadaveric induration by Ballantyne (quoted by Gray BJD 45: 498 1933) Many cases were seen during the siege of Leningrad (Antonov: JPed 30: 250 1947) Compare lipogranuloma, starvation edema, and edema neonatorum.

Scleredema such as occurs in adults may occur in a child.

Scleroderma is exceedingly rare in infancy; Dias and Woringer (BullsocfrançD 36: 960 1929) accepted only 3 cases as true ones.

Tropical Fat Liquefaction.—Castellani and Chalmers (Tropical Medicine Wood, 1929 p. 2233) described nodules containing liquid fat as being of common occurrence in the subcutaneous tissue of the arms, legs and abdomen of both European and native adults in the tropics; the liquid can be drawn off by needling. Compare fat necrosis in the newborn (p. 700)

Chronic Idiopathic Genital Edema occurs more often in males. The parts swell and remain swollen but are otherwise asymptomatic for some time, then gradually return to normal (Blechmann and Menard BSocPéd 31: 31, 1933)

General Idiopathic Edema has been recorded and may be due to abnormal salt metabolism it has occurred congenitally in association with abnormal hematopoiesis. Starved children may show anasarca, diarrhea, stomatitis, acrocyanosis and apathy promptly cured by food (Chvarria and Rotter: RevmédlatinoAm 23 1027 1939) Compare starvation edema.

Lymphangiectatic Edema has been described by Fromm (quoted by v Reuss: Diseases of the Newborn, Wood, 1929) As the edema subsided, the skin remained too loose. In Fromme's case the skin of the chest and back could be lifted in large fold like that of a young dog Such cases are of interest in comparison with cutis hyperelastica and the rare but remarkable instances of cutis pendula, being perhaps examples of v Recklinghausen's disease recognized early

EDEMA NEONATORUM

This affection of the newborn is characterized by subcutaneous, firm edema. It resembles sclerema, and the two are readily confounded. In edema, the sites of predilection are the eyelids and the dependent part of the body particularly the hands and feet. The affected parts are waxy looking and usually feel soft and doughy but they may be quite hard and indurated. Early in the disease, the skin is yellowish or livid in color, but later it generally becomes smooth, glossy and shining There is often associated icterus, and at times purpura and even gangrene. General anasarca is rare The temperature is often subnormal. Nephritis is an uncommon complication. There is no sclerosis or atrophy as in sclerema and the characteristic hidebound feature of that disease is absent.

Dumas (quoted by Holt Diseases of Children Appleton-Century 1940) considered the disease analogous to phlegmasia alba dolens and reported 13 cases in African native

infants, in whom were associated general edema depigmentation, photophobia and rashes. Adrenalin injections resulted in prompt benefit, along with optimum nutrition as in the treatment of pellagra. Feeble poorly nourished infants are the ones involved. Histologically one finds only edema. The prognosis is unfavorable, and relapses are common. Transfusions and antibiotics should save such babies. Compare starvation edema, and kwashiorkor (pp. 747 748)

DERMATOMYOSITIS

Dermatomyositis is an acute subacute or chronic disease of unknown origin, characterized by vague and indefinite prodromes, edema, dermatitis and *nonsuppurative myositis affecting numerous muscles. Fatigue anorexia, pains* and stiffness especially of the legs, fever and progressive muscle weakness are early features. In the acute cases walking is impossible and the head drops when the afflicted patient is lifted (Selander ActaMScand 138 187 1950) On the other hand the disease may be mild, evolve with chronicity perhaps show partial or complete remission. Tenderness of the muscles is present but variable in severity and atrophy ensues.

Dermal manifestations may resemble erythema erysipelas, urticaria, eczema or erythema nodosum. They generally appear over the affected muscles. The face especially the eyelids, and the extremities, especially the proximal portions are involved. Fever is moderate and remittent or intermittent. Sweating is a common symptom as is enlargement of the spleen. Involvement of the muscles of respiration and deglutition has led to bronchopneumonia or suffocation



Fig 1257 —Dermatomyositis, a fatal case. (Dr Onis George Hazel.)

In a summary of 40 cases affecting children, observed at the Mayo Clinic, Roberts and Brunsting (PostgradM 16 396 1954 abs YBD 1954, p. 222) listed the frequent early symptoms as malaise anorexia, loss of weight, fever irritability polymyalgia, and occasionally abdominal pain and vomiting. Insidiously progressive weakness may be the only one affecting the muscles of the shoulder girdle neck, lower trunk, pelvic girdle and quadriceps group. The head droops forward, and the patient can hardly raise his arms or rise from the lying to the sitting position. In the more advanced state he shows evidences of weakness of the diaphragmatic, intercostal, oropharyngeal and extrinsic ocular musculature The rashes are polymorphic, with recurrent edema of the face and extremities seen in the early stage, first in the eyelids and then extending over the cheeks, face, neck and shoulders. Characteristically there appear small, scaly bluish red plaques over the knuckles, elbows knees and ankles. The skin becomes pigmented and atrophic. Hypertrichosis is common. Subcutaneous tissues may show calcification. The heart may be involved as shown by electrocardiographic study and death from heart failure may occur. Biopsy of skeletal muscle taken from tissues with tenderness or doughy infiltration shows perivascular infiltration with lymphocytes, plasma cells, fibroblasts and a few polymorphonuclear leukocytes. These cells invade and separate the muscle bundles, the fibers of which are first edematous and later undergo vacuolar granular and hyaline changes, finally becoming homogeneous, to be replaced by fibrosis. Electromyography is a valuable diagnostic procedure revealing decrease in size amplitude and duration of the motor unit potentials on voluntary movement, while the number of action potentials is increased relative to the strength of contraction. Fibrillation potentials and increased irritability are found in resting muscle. The course of the disease in children is variable usually chronic. It is sometimes fulminant death resulting in a few weeks or months Roberts and Brunsting recommended in treatment physical therapy started early and cortisone or ACTH in the acute phase

The patient of Ingram and Stewart (BJD 46 53, 1934) developed pigmentation and atrophy of the skin, as well as symptoms of myasthenia gravis. Keller (ZtschrfKinderh 59: 531 1936) reported a girl 10 years old, whose symptoms were weakness, edema and an eruption resembling disseminated lupus erythematosus. He noted that 23 cases had previously been recorded as having occurred in children and 80 in adults. O'Leary and Wais-

man (ADS 41: 1011 1940) collated 40 Mayo Clinic cases, among which 11 were preceded by acute infection such as tonsillitis or influenza. Myositis was roughly symmetric the affected muscles being sometimes normal in consistency, sometimes doughy o tough and fibrous. Deep reflexes were diminished or lost. Involvement of pharyngeal, laryngeal, or respiratory striated musculature was of bad omen. Cutaneous changes not always present, included erythema, edema, pigmentation, sclerosis atrophy and efflorescences resembling lupus erythematosus and poikiloderma atrophicans vasculare. Half of their patients died. Scheuermann (AfDuS 178: 414, 1939) reported 10 cases and reviewed 263. Mucous membranes were affected in 70% of them. Dermatomyositis accompanied cancer of the lung in the 2 cases of Bouton et al. (Tórax : 417 1953)

Etiology—The cause is unknown, but st phylococci and streptococci along with focal infection may be significant. The relation to scleroderma is debatable. Dowling and Griffiths (Lancet 1 1424 1939) pointed to the similarities and noted the appearance of Raynaud s syndrome in some cases of both diseases. Keil (AIntM 66: 339 1940) nd Banks (NEngJM 225: 433, 1941) were impressed with the resemblances to systemic lupus erythematosus d periarteritis nodosa (see J 11.: 1159 1939) Calcinosis, scleroderma and symptoms of Addison's disease may also occur as in the patient of Talbott et al. (AIntM 63: 433, 1939) Calcinosis universalis was present in 4 of the 5 children studied by Hecht (JPediat 17: 791 1940) A coincidence, possibly a relationship, with malignant tumor was remarked by Dostrovsky and Sagher (BJD 58: 5., 1946) as had been noted in 3 cases by Bezecny (AfDuS 171: 24., 1935) and as was subsequently observed in 3 cases associated with visceral carcinoma by Sheard (AIntM 88: 640 1951) whose studies included 25 cases without malignancy An eruption on the face or hands was the initial symptom in over half of Sheard s cases, all of whom h d muscular weak ess and most of whom complained of muscle pains. Joint pains, dysphagia, serositis, edema, calci osis, cutaneous ind ration and Raynaud phenomenon were othe symptoms. Many patients had mild anemia, increased sedimentation rate albuminuria and EKG changes suggesting myocardial damage. While the disease usually had a gradual onset, in childre and young adults it tended to run a short course with high mortal ty a longer course with eventual recovery in older adults. Of 45 patients reviewed by Curtis et l. (J 150: 844 1952) 8 had associated malignant lesions and of these, 6 improved when their neoplasm wa treated. The symptoms of dermatomyositis developed in all 8 patients prior to the discovery of neoplasia. Hypertrichosis in a 0-year-old boy w the unusual occurrenc in the case described by Reich and Rei hart (ADS 57: 725 1948) A case wa recorded (ADS 68: 101 1953) in which Cushing syndrome develope l, and when adrenalectomy was performed both diseases involuted.

Pathology—Cha ges re found in the muscles, dermis, fat panniculus deep f scia d elsewhere. Th superficial portion of the dermis is little affected, but deeper one notes edema, congestion, hyaline degeneration of fibrous septa, and infiltration of septa and fat lobules with lymphocytic and epithelioid cells, plasma cells, and fibroblasts. Inflammatory infiltrate may replace large masses of adipose tissue. The cutaneous histologic cha ges are not specific (Kinney a d Maher: AmJPath 16 561 1940) nor are those of the muscles; the variability f the manifestations is such that doubt is justified as to whether dermatomyositis is a single clinical ent ty according t Jaeger and Grossman (AIntM 73: 271 1944) Similarities of histologic changes in scleroderma and dermatomyositis were stressed by Freudenthal (BJD 5.: 289 1940) In the muscle tissue, Pagel et al. (JPathBact 61: 403, 1949) observed (1) vacuolation and shrinkage, altered staining affinity and loss f striation, (2) increased numbers of myogenic nuclei surrounded by fragments of muscle substance and syncytium formation and (3) vascular changes with eosinophilic fibrinoid thickening of arteriolar walls, the homogeneous material being subendothelial, concentric o eccentric an l sometimes occlusive. Other organs are also involved (Wainger and Lever: ADS 49: 196, 1949) Peripheral vascular changes resembling those of thromboangiitis obliterans were described in the patient of Silverman and Powell (AmHeartJ 30 441, 1945) The relatively noninflammatory nature of the skin changes in dermatomyositis diff rs from the ma ked infiltrative alterations in poikiloderma atrophicans vasculare (Dowling and Freudenthal BJD 50 519 1938)

Treatment has been empirical, utilizing rest, massage and salicylates. Prostigmine disappointed Hendry and Anderson (Lancet 1 80 1939) Di hydrotachysterol 20 drops of 0.5% in oil by mouth twice a day seemed to explain the recovery of Costello s case (ADS 48 429 1943) and another patient of his (ADS 60 922, 1949) showed remarkable improvement on diphenhydramine 400 mg daily A patient with recurrent episodes of streptococcic disease was palliated for a time with sulfonamides but eventually died of toxemia (Lamb JOklaMA 37 5 1944) Good improvement followed the use of vitamin C thyroid, wheat germ oil, cod liver oil, x ray therapy and physical therapy in Cannon s case (ADS 51 287 1945) Madden (ADS 53 169 1946) recommended penicillin intravenously Testosterone may help (Lamb et al. ADS 57 785 1948) Para-aminobenzoic acid, having been found helpful in systemic lupus erythematosus, was tried by Zarafonetis et al. (AIntM 85 27

1950) whose 2 patients with dermatomyositis improved during prolonged therapy with this drug when given in doses as great as 2 Gm. every 2 hours. A severe case affecting a young man was dramatically arrested and apparently cured by ACTH, according to Oppel et al. (AnnIntM 32: 318 1950) and gratifying remission followed the use of ACTH in another treated by Williams and Bowler (Lancet 1 1063 1951) Despite the initially high white blood cell count the acute case treated by Clein (BMJ 2 1357 1953) with cortisone and ACTH underwent remission.

Poikilodermatomyositis is the name applied to cases with features of dermatomyositis in which atrophy of the skin also occurs. Such were described by Petges and Clégat (AnndeD 7 560 1906) clarified by Guy et al (ADS 40 867 1939) Areas of skin became inflamed scaly then atrophic with telangiectases and pigmentation. Sclerosis and calcinosis may also occur in these cases (Hopkins ADS 39 761 1939, Horn ADS 44 1086 1941; Kanee ADS 50 204 1944) High creatinuria due to destruction of muscle tissue is a common feature observed Traub (ADS 47 734 1943) whose case resembled systemic lupus erythematosus. Calcinosis accompanied poikilodermatomyositis in a young Brazilian woman studied by Silva et al. (ADS 68 588 1953)

See Wagner (ArHeilk 4 283, 1863) first description Unverricht (DMedWchr 17: 41 1891) named the disease, according to Lane (SouthMJ 31 28 1938); Urbach (ArDerS 163 27 1930), case, myositis and erythroderma resembling leukemia cutis Sydenstricker and Thomas (ArIntM 8 889, 1938) case with high eosinophilia, Wolf and Wilens (AmJPath 12 235 1936) 2 cases Greenaway et al. (BJD 49 203 1937) case with utopsy, Sheldon et al (Lancet 1 82, 1939) young man died with petechia and arteriole thrombi; Kellogg and Cunha (CalifM 50 237 1939), case followed vaccination, associated with rheumatic heart disease; Hazel and Hull (SouthMJ 33 809 1940) 2 fatal cases in children, with pathologic changes in skin, muscles and heart Lewis (BJD 52 233 1940) young girl with Raynaud symptoms and digital gangrene Fraser (BJD 54: 266, 1942) utopsy on woman Holmes (BMJ 2 511, 1946), acute nonsuppurative myositis with bullous erythema multiforme Packer (BJD 62 494, 1950) case, boy palliated with physiotherapy Roberts (AD 71: 372, 1955) discussion of 6 cases.

RELAPSING FEBRILE, NODULAR, NONSUPPURATIVE PANNICULITIS

The lesions in this rare disease are irregular or rounded bluish or erythematous nodules of 0.5 to 10 cm. diameter They appear at irregular intervals of weeks or months without relation to season. Fever and malaise accompany their appearance The lesions occur mainly on the thighs but may be situated on the trunk or extremities. As they undergo evolution, subcutaneous atrophy results in concave depressions. There is a disease, then wrote Christian (AIntM 42 338 1928) characterized by recurrent attacks of fever associated with peculiar nodular inflammation of the subcutaneous tissue. Some of the fat tissue undergoes necrosis much of it becomes infiltrated with lymphoid and plasma cells. Macrophages take up fat in fine droplets. A few foreign body giant cells form. There results in time atrophy of the inflammatory nodule leading to depression of the overlying skin, without suppuration

The characterization by Weber (BJD 37 301 1925) was classic and led to the designation of the affection as the Weber-Christian Disease Binkley (J 113 113, 1939) noted that 11 of the 13 reported cases were females, among whom obesity was common. Sterile yellow-green, mucoid material was aspirated from lesions, some of which involved the breast in his patient and resembled traumatic lipogranuloma. In the earliest lesions the infiltrate was composed largely of polymorphonuclear leukocytes in the man studied by Lever (ADS 59: 31 1949) Early lesions resembled morphea in the young girl of Hazel and Lamb (JOklaMA 33 1, 1940) While adult women are predominantly the victims, the patient of Gilchrist and Ketron (BullJHH 27: 291, 1916) was a girl 8 years old. The patient of Boyd wall (JCutD 36 145 1918) a girl of 10 years, showed involvement only of Scarpa's triangle and an area over the tibia. Christian's patient was a girl of 25 whose picture is reproduced here.

Liquefying Nodular Panniculitis was exemplified by a woman reported by Shaffer (ADS 38: 535 1938) who developed deep, painful woody nodes in crops of 2 or 3 at a time involving the extremities and buttocks; the lesions in 7 to 10 days became cystic and broke through the thinned and reddish overlying skin to discharge 1 to 4 ounces of oily liquid, and then healed with the formation of depressed scars covered with atrophic skin. In a patient of Ayres (ADS 54 590 1946) the lesions would gradually enlarge making dull red elevations as they reached the surface become fluctuant discharge, and heal with scarring The fluid was sterile in a similar case of Schwartz (BJD 64: 291, 1952). The

appearance of nodules which underwent liquefaction and discharge was related to the menstrual cycle in 1 of the 3 patients of Jones et al. (SouthMJ 43: 92, 1950) The other patients were infants with fat necrosis of the newborn.

Etiology—The cause is unknown (Bailey J 109 1419 1937) Diabetes mellitus complicated the 4 cases of Machacek (JID 10 215 1948) While the disease was attributed to allergy by Eisaman and Schneider (J 146 1417 1951) trauma, they thought, was an important localizing factor The laboratory data on 44 cases reviewed by Bendel (ADS 60 570 1949) were of no revealing

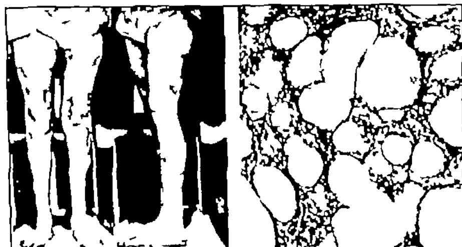


Fig 1288—Relapsing, febrile, nodular nonsuppurative panniculitis. (Christian AIntM 42 338, 1928.)

Fig. 1289—Histologic picture of panniculitis. (Bailey 109 1419 1937)

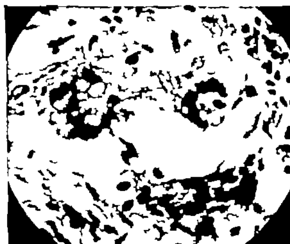


Fig. 1290—Lipophagic giant cells in panniculitis. (Dr Stuart C. W y)

significance. Leukopenia has been found in about half the cases on record (Johnson and Pliee APath 48 287 1949) Hepatic disease is a constant finding at autopsy, according to Taylor et al. (SouthMJ 46 1163, 1953)

Treatment.—*Sulfapyridine relieved the case of Arnold* (ADS 51 94 1945) for a prolonged period, but relapse fever and increase of sedimentation rate appeared when the drug was discontinued. Penicillin apparently cured a patient of Zee (J 130 1219 1946) after sulfonamide had failed. Cortisone was significantly helpful in 2 cases observed by Harrison and Saxton (JMoMA 50 427 1953); Asel and I had similar experience with a woman whose course was reminiscent of periarteritis nodosa.

See Pfeifer (DeutArchKlinM 50: 438, 1892) Alderson and Way (ADS 27 446, 1933), case Keil (BJD 47 612, 1935) distinction between febrile and nonfebrile panniculitis; Reed and Anderson (CalifWM 47: 325, 1937), case Cummins and Lever (ADS 38 415, 1938), 3 cases, bibliography; Tilden et al. (ADS 41: 681, 1940) 2 cases; Fraser (ADS 45 818, 1942) case affecting arms especially Graham (ADS 50 133, 1944) case (?) nonscarring Ldt (J 140, 1220, 1949), brief review Hallahan and Klein (AnnIntM 34 1179, 1951), case and review Birrell (MJAustral 2; 7 1952), Myco. leprae possibly causative, found in 3 cases Slepian and Slade (NYSJM 52 697 1952) case showing bleeding tendency; Dorfman (ADS 68: 692, 1953) mediastinal involvement Sanford et al. (AmJDisChild 85 156, 1953) onset at age 6 months, *Strept. viridans* in anaerobic cultures Beerman (AmJMedSci 225 446, 1953) review bibliography 14 fatal cases Macdonald (BMJ 1 377 1954) with coronary thrombosis in old woman Pokorny and Hellwig (JKansasMS 55 70 1954), case initiated by trauma, serum lipase elevated Rubens-Duval and Desse (SemHop 30 316, 1954) "pararheumatic.

ATROPHIC DERMATOSES OF UNDETERMINED CAUSE

CLASSIFICATION OF ATROPHIES OF THE SKIN

Types of Atrophy have been classified by Oppenheim (HandbHuG 8 pt. 2, 500 Springer 1931) This, as modified by Sweitzer and Laymon (ADS 31 196 1935 cf. Marquardt DZtschr 75 170 1937) divides atrophies among those which are present at birth and those which are acquired the latter being subdivided into those associated with inflammation and those not associated with inflammation.

Congenital Atrophies
- Congenital ectodermal defects (p. 1056)
- Congenital nevoid atrophy
- Diffuse universal atrophy

Acquired Atrophies
- NONINFLAMMATORY
  - Senile
  - Externally influenced
    - Degenerative senile (see keratoses, p. 11 9)
    - Xeroderma pigmentosum (p. 1255)
    - Roentgen and radium atrophy (p. 111)
    - Atrophic striae striae distensae
    - Pressure and occupational atrophy
  - Internally influenced
    - Hunger marasmus, cachexia
    - Nervous and trophic influences
- INFLAMMATORY
  - Progressive chronic atrophic dermatitis
  - Diffuse atrophic dermatitis
  - *Acrodermatitis atrophicans*
    - Macular atrophic dermatitis (primary macular atrophy)
    - Poikiloderma
  - Blepharochalasis
  - Kraurosis
  - Atrophy consequent to scarring inflammatory diseases (secondary macular atrophy) lupus erythematosus, syphilis, leprosy tuberculosis, lichen planus, lichen sclerosu et atrophicus, scleroderma, morphea, pellagra.

DIFFUSE IDIOPATHIC ATROPHY OF THE SKIN

Buchwald (VirtljschrfD 10 553 1883) was the first to describe an authentic case of idiopathic atrophy of the skin, according to Irvine (J 41 296, 1913) A few years later Kaposi called attention to the fact that the atrophy in these cases was probably not primary but rather represented dermatitis passing into atrophy As Finger and Oppenheim (Die Hautatrophien, Vienna, 1910) suggested many cases formerly classed among the idiopathic atrophies can be placed in definite groups of their own the lesions are symptomatic rather than idiopathic.

DERMATITIS ATROPHICANS DIFFUSA (UNIVERSALIS) is the title which applies to cases involving large areas or the entire body

DERMATITIS ATROPHICANS MACULOSA —Only small, circumscribed areas are involved.

ACRODERMATITIS CHRONICA ATROPHICANS was the descriptive term first used by Herxheimer and Hartmann (AfDuS 61: 57 1902 see JCutD 23: 241, 1905

29 257 1911) according to Sweitzer and Laymon (ADS 31 196 1935) who reviewed Oppenheim s classification. Many authors classify all cases of diffuse idiopathic atrophy as acrodermatitis chronica atrophicans. Oppenheim, however limited this name to cases characterized by (1) doughy infiltration at the onset, (2) the presence of ulnar bands, (3) the localization on the extensor aspects of the extremities, especially the knee, elbow and finger joints, and (4) the absence of involvement of the entire body The face and the palms and soles are not involved and the trunk almost never Sweitzer and Laymon described the special features of the diseases:

The ulnar bands frequently appear in the early stage of infiltration, extending from olecranon to wrist on the medial surface of the forearm. Doughy or firm, and reddish in color they may disappear and be replaced by atrophy Rarely they are found in the region of the knee near the ankle or along the radius. Fibrous nodules may occur appearing painlessly in the subcutaneous tissue over the extensor surfaces, by predilection, on the elbows, knees and wrists, nut to pea size singly or in groups. Scleroderma like changes occur in about a third of the cases, most often on the lower part of the leg and dorsum of the feet The glazed indurated areas may ulcerate Some cases are associated with arthritis deformans and bone atrophy



Fig. 1191—Acrodermatitis chronica trophicans, associated with arthritis deformans. (Sweitzer and Laymon ADS 31: 196, 1935.)

Atrophy of mucous membranes has been observed but is of extreme rarity Macular atrophy with ballooning is described. Associations with localized amyloidosis, melanosis, and multiple xanthomas have been recorded Sweitzer and Laymon s cases illustrated many of these features. They were able to determine no etiologic feature or availing therapeutic measure. Absorption of arsenic spray may have been significant in cases of Brueckmann (YBD 1940 p 167)

Finger and Oppenheim (1910) considered the macular and diffuse dermatitis atrophicans cases to be due to an internal causative agent acting on a predisposed skin, and th crodermatitis atrophicans cases t be d e to an external causati agent, such as, particularly mechanical chemical or thermal injuries, acting on a predisposed skin. Compare glossy skin, etiology The influence of disseminated vascul or rteriole disease on a rvea of the kin deserves consideration. I arteriosclerosis, hyaline subendothelial change of the fferent arteriole of the glomus transforms it into an incontractile cond it which constitutes detour of arterial blood into the veins, according to Popoff (Bull histolappliq 12: 156 1935) as a result, stasis and anoxemia lead to sclerosis and trophy of the cutaneous appendages. In a number of patients, the thymol turbidity test was positi and the sedimentation rate high (Koskinien; abs YBD 195., p. 311)

Interesti g cases exemplifying various types were presented by Schmitt et al. (ADS 40: 674, 1930) Familial i cidence the patients being sisters, was noted by Director and Bluefarb (ADS 46: 480, 1942) The entire skin became involved in Graham s patient (ADS 50: 255, 1944) Montgomery and Sullivan (ADS 51: 32, 1945) reviewed 45 Mayo Clinic cases of acrodermatitis chronica trophicans, stressing histologic studies. Acroder

matitis chronica atrophicans followed sunburn and affected only the right upper extremity in the case of Machacek (ADS 54 494, 1946) Anaplastic carcinoma developed on the affected leg of a patient of Lewis and Sachs (ADS 63 790 1951)

Acrodermatitis chronica atrophicans is to be differentiated from scleroderma, particularly the edematous type. The health is usually little affected. The progress of the disease is generally slow but progressive for a time after which it remains relatively stationary The changes are permanent.

Therapy is symptomatic and palliative Warm baths, galvanism and massage have been recommended Various endocrine and vitamin preparations appear to be worthless here Elimination of focal infection affords something to do Penicillin in large dosage was said to be beneficial by Witten (JID 16 193 1951) but his experience has apparently been unique. The administration of cortisone 25 mg b.i.d stopped the progress and itching of the disease in a patient of mine Chloroquin helped one of Huff (AD 72 132, 1956)

MISCELLANEOUS ATROPHIES

Atrophy involving the tongue and mouth was described by Hazen (JCutD 34: 881, 1916) Peculiar congenital atrophy with reticular pigmentation was observed by Engman (J 105: 1.52, 1935); compare Werner s syndrome Anetoderma in an infant, large striae developing on the thigh following an insect bite which provoked urticaria, was recorded by Pierini and Basso (RevArgentD 20 49 1936) A hereditary pigmentation of the lower third of the leg associated with atrophy was noted by Engman (ADS 8: 483, 1923)

Trauma from the use of a pneumatic drill damaged the subcutaneous fat of the abdomen and caused atrophic lesions in the patient of Johnson (ADS 57 1046 1948). A woman who suffered for 40 years from widespread and severe atrophy of the skin developed lymphadenopathy of the neck; the nodes were removed and diagnosed histologically as Hodgkin s disease, and after their removal the dermatosis disappeared, reported Ormsby (ADS 61 1031 1950)

See also Alopecia cicatrisata, Congenital ectodermal defect, Dermatitis medicamentosa from insulin, Dermatomyositis, Folliculitis ulerythematosa reticulata, Glossy skin, Lichen planus atrophicus, Lichen sclerosus, Lupus erythematosus, Macular atrophy Panniculitis, Poikiloderma, Scleroderma, Ulerythema ophryogenes.

Atrophoderma Albidum (Kaposi) is a stocking-like type of atrophy affecting the extremities, which begins in early childhood, generally on the lower limbs. It is a symmetric thinning rendering the parts sensitive and easily damaged, and is probably a congenital defect (Pusey Principles and Practice of Dermatology Appleton, 1926 p. 945). Compare Epidermolysis bullosa, dystrophic.

Poikiloderma Congenitale is the name given by Thomson (BJD 48 221 1936) to a condition which began in infancy on the buttocks and cheeks of 3 girls, 2 of whom were sisters Pinkish swellings of the skin evolved into a telangiectatic network with atrophic white interstices. The network became slowly pigmented. There was no mucosal change The case of Chiale (abs YBD 1937 p. 233) was identical except for the absence of a bony anomaly *noted by Thomson. Congenital cutaneous* dystrophy was the name under which Rook and Whimster (BJD 61 10 1949) reviewed 11 cases of this disease of which 9 patients were female.

It begins during the first year of life with tense red swellings on the cheeks, hands feet and buttocks, later perhaps on the forehead, ears, forearms and legs. Irregular brownish pigmentation appears on these areas and also usually on the thighs and the inguinal and axillary flexures. By the age of 10 or 1 years crust develop on the bony prominences The hair is sparse and eyebrows and lashes scanty or absent. Dental development is likely to be defective The patient is usually small and slender and manifest various skeletal abnormalities The atrophic skin may become in later life the seat of epithelomatous changes. Distinction is to be made from dyshormonal dermatitis, xeroderma pigmentosum and Rothmund s syndrome.

Cutis Marmorata Telangiectatica Congenita.—Tonseth (NorskMagfLaegevid 96 891 1933) described a newborn girl with an obscure dermatosis like that of the patient of Lohuizen. There was general dilatation of the superficial veins, mainly of the head, so that the appearance of the skin was marmoraceous. Malnutrition was present, and elongated areas of necrosis following the direction of the veins were observed to heal with scarring.

Atrophia Maculosa Varioliformis Cutis is the name under which Heidingsfeld (JCutD 36 563, 1918) described a patient in whom there spontaneously appeared on the cheeks sharply defined shallow pitted scars most of them round, some of them linear or rectangular without inflammation or pigmentation. Sweitzer (ADS 7: 403, 1923) saw a similar case and another was recorded by McCorriston and Ross (ADS 64: 69 1951). There was no similarity to folliculitis ulerythematosa reticulata. The patients, a man and 2 women, have been adults.

FOLLICULITIS ULERYTHEMATOSA RETICULATA

Ulerythema acneiforme atrophoderma reticulatum symmetricum faciei, and atrophodermie vermiculée are among the names under which has been described a symmetric eruption limited to the cheeks, occurring in young persons,





Fig. 1192.—Folliculitis ulerythematosa reticulata. (Dr George Miller MacKee.)

Fig. 1193.—Folliculitis ulerythematosa reticulata, showing scar of removal of sclerosing type of basal cell carcinoma, which appeared when the boy was 18 years old.



Fig. 1194.—Folliculitis ulerythematosa reticulata, showing deformity of hair follicles, atrophy of sebaceous glands, and inflammation and sclerosis of dermis. (Dr George Miller MacKee.)

and consisting of numerous, closely crowded, small areas of atrophy separated by narrow ridges so as to produce a reticulated, honeycomb or network appearance (MacKee and Parounagian. JCutD 36: 337; 601, 1918). The individual atrophic areas are pitlike, abrupt, and about 1 mm. in depth, and they range from 0.25 to 2 mm. across. In places, two or more depressions may

unite to form areas of perhaps 3 sq mm., or even larger There are a few small comedones, both in the depressed areas and in the ridges. A number of milium bodies are sometimes noted in the ridges. The skin covering the narrow partitions or ridges is on a level with that covering the unaffected portion of the face. The skin seems somewhat waxy stretched, more resistant, harder than the normal skin. The entire affected area may be irregularly erythematous. The disease may exist with or without notable inflammation. It begins in early youth and commonly has undergone its complete evolution, with permanent scarring before middle age. No effectual treatment is known.

MacKee and Parounagian described 2 cases in which the eruption was present over the greater part of both cheeks and symmetrically located. One of the patients was a girl 16 years old, the other a boy of 9 years. In the former the lesions had been present for 8 years, in the latter for 3 years.

The microscope showed a slightly atrophic epidermis with loss of papillation. Inflammation in the dermis was manifested by vascular and lymphatic dilation, congestion, edema, and perivascular and perifollicular infiltration of small round cells. Degenerative changes in the connective tissue were noted. They apparently ended in atrophy and retraction. Underdevelopment of sebaceous glands and overdevelopment of hair follicles were interpreted. Horny cysts derived from the hair follicles were scattered throughout the cutis some of them were connected to the hair follicles by a slender epithelial bridge and some were completely isolated.

Darier (BullsocfrançD 27: 345 1920) reported cases of vermicular atrophy of the cheeks with follicular keratoses. Burgess (BJD 44 357 1932) described the slow evolution and disappearance of comedones as adulthood developed. Winer (ADS 31 931, 1930), seeing similarity to the sebaceous nevus suggested that the process is a nevoid one with atrophy in the terminal stage

'Atrophoderma reticulatum is the inclusive title Winer preferred for such disorders, while honeycomb atrophy was the designation selected by Savatard (BJD 55 50 1943) whose patients were twin sisters not uniovular Compare ulerythema ophryogenes.

The cause of the disease is unknown. It is distinctly different from White s linear comedo nevus. It differs from grouped comedones (q.v) although grouped comedones with atrophy and resorption instead of foreign body reaction and acneiform pustulation would produce a similar picture Differences from acneic scarring are readily discernible A family in whom appeared this anomaly, neurofibromatosis and congenital heart disease was described by Carol et al. (Dermatologica 81: 345 1940) the skin condition was interpreted as a congenital hamartoma.

Patients first seen in 1918 were reviewed, along with all others then on record, by MacKee and Cipollaro (ADS 57 231 1948) and reticulated atrophy still persisted in them they collected 28 instances of the disorder Morphea like basal cell epitheliomas of the malar skin of both cheeks developed before he was 20 in a boy whose case I followed.

See Sutton (DWchn 56 245 1913) symmetric dermatitis of the face with associated atrophy, Bruck (AfDuS 162 100 1930) Goldberg (AfDuS 174 591 1936) De Moon (ADS 39 1082, 1939) case Groneberg (AfDuS 181 495, 1940) 14 cases reviewed, Ingels (ADS 43 388, 1941), case resembling comed nevus Senear (ADS 44 943, 1941) affecting sisters Duckworth (BJD 55 57 1943) case, histology; Brody (ADS 63 231, 1951) case Vogel (DWchn 122 469 1950) in 4 sisters.

ULERYTHEMA OPHRYOGENES

Described by Taenzer (MonatshPrakD 8 197 1889) this rare condition has features suggestive of seborrheic dermatitis, keratosis pilaris and folliculitis decalvans, according to Stelwagon (Diseases of the Skin, Saunders, 1921, p. 1062) Slight redness scaliness and thinning of hairs begin in the outer part of the eyebrows some hairs are broken off at the mouth of the follicles, while others are atrophic and loosened. The condition may progress toward the inner half of the brow or it may remain confined to the outer part. With progression horny projections at the mouths of the follicles make their appearance As this curious dermatosis continues, the features of atrophy and pitting are superadded to the previous symptoms, with permanent loss of the involved hairs. Rarely the condition spreads to involve the scalp forehead and cheeks and the areas of predilection of keratosis pilaris. The disease is extremely chronic and persistent it elects blonds, and both children and adults may be affected.

The follicular hyperkeratosis was responsive to vitamin C in a patient of Gyürki (AfDuS 175 707 1937) It did not respond to vitamin A in the case of Hecht (ADS 51 41 1945) who would diagnose as ulerythema ophryogenes the cases starting with

hyperkeratosis in the eyebrows in early youth, and as keratosis pilaris rubra atrophicans faciei the cases which show keratosis pilaris, erythema and consecutive scarring starting on the temples in front of the ears.

A case of keratosis pilaris limited to the face described by Anderson (ADS 49: 81, 1944) was somewhat similar Ulerythema ophryogenes was congenital in the patient of Kleine-Natrop and Liedeke (ZtschrHuG 5: 284, 1948) It was typical in the little boy of Zakon and Goldberg (ADS 64: 785, 1951), with diffuse redness and alopecia of the eyebrows and small, discrete, elevated, round, horny erythematous, pinhead-size papules at the mouths of the hair follicles. This child also presented an enlarged liver and manifestations of difficulty in metabolizing vitamin A and carotene. See Brünauer (HandbHuG 8: pt 2, 122, Springer 1931)

Such patients appear to deserve study from the standpoint of establishing nutritional and endocrine balance Compare Ronchese s case (described under milia Fig 1565 p. 1168) and Keratosis pilaris rubra atrophicans faciei therewith discussed.



Fig. 1295—Macular atrophy due to syphilid. (Dr Adolph Loveman.)
Fig. 1296—Morphea, trophia, "en coup de sabre. (Dr James A. Mitchell.)

MACULAR ATROPHIES

Anetoderma of Jadassohn begins with little circumscribed, erythematous macules, which fade at the center and form circular lesions within which atrophy progresses. The surface becomes shiny, white and crinkly and the central region may protrude baglike with reddish or yellowish coloration (Andrews Diseases of Skin, Saunders, 1946) This variety of primary macular atrophy has an initial erythematous stage (Oppenheim and Cohen ADS 50 64 1944) The lesions in a woman 32 years old, reported by Obermayer (ADS 54 591 1946) began at age 6 and were erythematous at first, were from 5 to 15 mm. in diameter and healed with fine, wrinkly atrophy and depigmentation they were scattered over the neck, sternum, extensor aspects of the arms, flexures of the forearms, the lower back and the front of the thighs. The lesions in a young woman observed by DeOreo (ADS 63 635 1951) began on the arms during the first month of pregnancy Endocrine therapy may influence its progress, which is reminiscent of localized myxedema, in an occasional case like that of Foerster (ADS 34 725 1936) whose patient manifested Fröhlich s syndrome

Red plaques of 1 to 5 cm diameter located mainly on the extremities of a hypoestrogenic female, healed during her pregnancy and later spectacularly abated under stilbestrol therapy leaving atrophic scars (Sweitzer and Winer: ADS 54 581 1946)

Multiple Benign Tumorlike New Growths (Schwenninger Buzzi type of macular atrophy) —See p 1105

Secondary Macular Atrophy is the result of destruction of the elastic tissue by inflammatory infiltration, however diverse the causes of this may be (Scull and Nomland ADS 36 809 1937) Syphilis is a common cause (Wise ADS 9 509 1924 Schwartz BJD 62 463 1950) Elastic tissue destruction may result from subclinical inflammation Xanthoma tuberosum on resorption may leave atrophic residuals (Hubler ADS 50 211 1944) See also Dermatitis medicamentosa arsenic Epidermolysis bullosa White-spot disease.

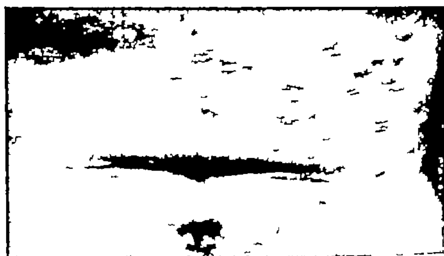


Fig. 1297—Macular atrophy skin of abdomen, due to syphilis. (Dr O G Costa.)

HEMIATROPHY

Symptoms.—Romberg's disease may include the entire half of the body—some 23 cases of total hemiatrophy had been recorded by the time of the extensive review by Archambault and Fromm (ANeurol 27 529 1932)—and it may include more than the usual fifth nerve distribution. Neither side predominated and there were known some 27 cases of bilateral involvement.

Hemiatrophy of the face is a rare striking abnormality usually of early onset without predilection as to sex, and involving all structures of the affected side although the skin may escape The muscles do not lose their function, but the subcutaneous fat is greatly diminished and the bones themselves are actually smaller

Archambault and Fromm found that the onset is often in the second decade but may take place in the first year or may be delayed even until middle age The atrophic process may begin at any point about the orbit angle of the mouth, nose or malar area it spreads gradually or rapidly over the entire half of the face it may come to a standstill at any stage Falling or blanching of the hair in the affected areas is common. An abnormal pallor is usual and may signify that the vessels are atrophic. Neuralgic pains frequently accompany the atrophy They may precede its onset or may occur during its course and they are associated especially with atrophy in the trigeminal area. Tauber and Goldman (ADS 39 696 1939) said that more than 400 cases of various stages of progressive hemiatrophy had been published. Histologic changes of the skin are meager but the scalp regions affected show alopecia

Etiology—Hereditary influences are not significant according to Archambault and Fromm. Previous infectious diseases have been remarked, but these as well as local infectious processes are of quite doubtful connection. Association with convulsions, facial palsy, epilepsy and organic disease of the central nervous system have all received attention. Osborn (ADS 6: [illegible]) suggested that hemiatrophy is a phenomenon of localized scleroderma, and dermatologists have inclined toward this opinion, supported by O'Leary and Nomland (AmJMedSci 180: 95, 1930) in their review of 103 cases of sclero-

derma, as well as by Eller (ADS 18: 766, 1928) The skin is not bound down, however but is free and movable; furthermore, it is to be admitted that some cases of scleroderma have undoubtedly manifested symptomatic hemiatrophy Some cases seem actually to hav been produced by damage to the cervical sympathetic nerves, a fact favoring the hypothesis of a sympathetic nervous origin of the disease. Merritt et al. (JPediat 10: 374, 1937) demonstrated, in patients with hemiatrophy shadows in roentgenograms of the head such as are produced by calcification of cavernous hemangiomas. The external lesions likewise bore considerable resemblance to the scarring which results from spontaneous atrophy of hemangioma (see p. 1115)





Figs 1298 and 1299 —Hemiatrophy of face of a girl 12 years old X rays revealed intracranial calcification (Merritt et al. JPediat 10 374, 1937)

Differences of opinion regarding the etiology of facial hemiatrophy, regarding it as angiomatous, sclerodermatous or of sympathetic nerve origin, are reconcilable on a neurologic basis. The theory of abnormality of the autonomic nervous system carries the preponderance of current evidence. The patient of Finesilver and Rosow (J 110: 366 1938) showed differences in the sweating of the two sides and sparsity of hair on the affected side.

Treatment.—If distortion has completely evolved and is at a standstill cosmetic injections of paraffin may be considered. Archambault and Fromm preferred early periarterial sympathectomy Plastic surgery has something to offer (Kazanjian and Sturgis J 115 349 1940)

BLEPHAROCHALASIS (ATONIC PTOSIS)

This is a disease of the upper eyelids which is characterized by permanent swelling of the lids, with great thinning of the skin and bagginess of the lids. As a rule the involvement is bilateral. The disease is usually found in young persons as an intermittent swelling of the upper lids, wrote Denedict (J 8 1735 1926)

It makes its appearance soon after puberty as a transient edema of the upper lids lasting for a few hours, the attacks coming on at intervals of a few days or a few weeks. Succeeding attacks last longer and appear more frequently till permanent swelling of the lid with great thinning of the skin and bagginess of the lids results. The bagginess and atrophy of the skin are the characteristics of the disease by which the name blepharochalasis is suggested. The onset is usually insidious, and its early manifestations are over looked or misinterpreted. The diagnosis becomes clear only after permanent changes are brought about in the lids. The disease is more commonly found in young girls but has been observed in young boys and even in old men. Fuchs observed it in the lids of a man past middle life. It has been recognized in later life in persons who have had the swelling of the lid and trophic appearance of the skin since early youth. Blepharochalasis is to be found in stages. The first is the intumescent state or stage of edema. The early

attacks of swelling resemble those of angioneurotic edema and last, usually for from 3 to 4 days without pain, and with only slight redness of the skin. After several attacks of swelling one of two things occurs (1) The swelling becomes constant with bagginess of the skin of the lid so that loose folds hang down over the margin, giving the appearance of water-filled bags, with the skin altered slightly in color very thin and slightly folded or wrinkled or (2) the swelling disappears entirely or occurs for only short times, at intervals of weeks or months, and the skin becomes reddish brown and wrinkled, and is thrown into horizontal folds resembling brown, wrinkled cigaret paper. The latter condition causes less interference with vision but may be accompanied by true ptosis. The stage of wrinkling is the end stage of the disease.

About 80 cases could be collected for review by Alvis (AmJOphth 18: 235, 1935) See Gunther (AmJOphth 18: 832, 1935) case; Hadley (RockyMtMJ 37: 517, 1940) dermatolysis palpebrarum. The onset was at about the time of puberty Benedict found, and males and *females* were affected equally By the time loosely hanging folds have developed, the septum of the orbit may relax and the fat prolapse the lid skin then hangs in full heavy transverse folds, weighted down and narrowing the fissure, a condition known as fat hernia. The adipose and atonic types occur in 4:3 ratio. Pathologic examinations have *revealed* only atrophy and evidences of low-grade inflammation.

The cause may be eczematous dermatitis with secondary atrophy Plastic surgery may be used. It may require repetition if attacks are still occurring.



Fig. 1300.—Blepharochalasis. (Benedict J 87: 1736, 1926.)

POIKILODERMA

The name is of Greek origin signifying skin that is varicolored.

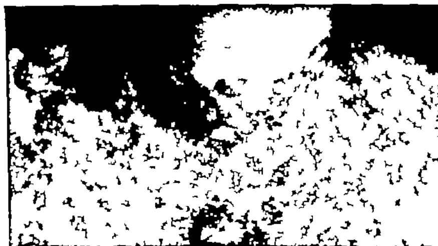
The poikilodermas can be divided into 2 main types, that of Jacobi, with the inclusion of poikilodermatomyositis (p 1014) and that of Civatte which is identical with Riehl s melanosis (p 790)

Poikiloderma Atrophicans Vasculare of Jacobi.—Two cases of this rare disorder were discovered in America by Lane (ADS 4 563 1921 8 373, 1923 15 621 1927) who found that, of 14 cases, 9 occurred in males, and 5 in females. The ages ranged from 6 to 41 years. The dermatosis is complex and of slow evolution. It is characterized in the early stages by telangiectasis and pigmentation and, later capillary hemorrhage with atrophy *similar to that* seen following x ray burns.

The clinical picture was well summarized by Dowling and Freudenthal (BJD 50 532 1938) most cases have been reported after the dermatosis has existed for many years so that description of early stages is obtained *only by* the patients accounts. Red patches, one or a few in number appeared in various situations with apparently some predilection for the large flexures and axillary folds. In some cases the eruption has gained gradually on the *surface* so as to occupy eventually the greater part of it. In others *it has occupied*, when first seen, a number of circumscribed areas. The face is often spared but is edematous when involved edema is absent when *involvement is not of* the face. The color ranges from bright red to a brownish red or brown. The eruption is made up of telangiectases tiny petechial hemorrhages, pigmentation depigmentation and miliary lichenoid papules and is generally covered



Fig. 1301.—Poikiloderma. In this man, 64 years old, there appeared 34 years previously lesions of one forearm; during the next 10 years reticulated reddish areas, simulating chronic roentgen dermatitis, developed over the body without systemic symptoms. Microscopic study by Dr. Fred Weidman revealed thinning of the epidermis, replacement of basal epidermal cells by cells of squamous type, and destruction of the basement membrane by extension of round-cell infiltration into the epidermis from the dermis, which was infiltrated with lymphocytes and endothelial cells; the arterioles were hyperplastic and had thick walls. (Hazel: ADS 40: 175, 1939.)



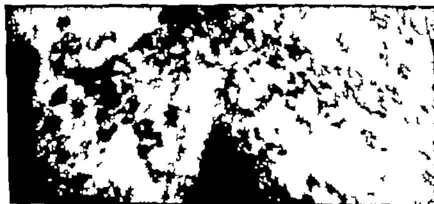


Fig. 1302.—Poikiloderma atrophicans vasculare: anterior neck and sternal regions of an old woman.

with strongly adherent scales. The skin is atrophic and in places pleated like cigaret paper Sclerosis is never found. The elementary lesions are arranged in a variegated manner sometimes evenly distributed and closely set so as to produce a considerable depth of color exceeding that seen in dermatomyositis sometimes the distribution is reticular large or small meshes enclosing areas of normal, erythematous or atrophic skin Ulcers or the scars thereof have been seen in a few cases. There are no general symptoms, but the cutaneous changes give rise to sensations of pricking tingling or itching or especially in winter to discomfort and pain caused by cracking of the dry skin. The disease is slowly progressive

In treatment grenz rays helped a patient of Dostrovsky and Sagher (ADS 51 182 1945) and x rays should be about as useful as in mycosis fungoides



Figs 1203 and 1204.—Poikiloderma atrophicans vasculare. (Lane ADS 4 [illegible] 1921 5 371 1922.)

(q v) A patient who also had syphilis was apparently cured of both diseases by arsenicals and fever Kalz and Hoogstraten (ADS 53 333 1946) reported. An old woman I saw in 1944 was much benefited symptomatically by cortisone

Histologically there are early perivascular round cell infiltration, dilation of the vessels, and pigmentary changes in the skin Later one finds atrophy of collagen with degeneration and ultimately disappearance of elastic tissue

Lane's patient died of lymphosarcoma. Another case which [illegible] mycosis fungoides [illegible] described by Oliver (ADS 33: [illegible] 1936) and this is th[illegible] outcome [illegible] according to Hazel (ADS 40: 70, 1939) The patient of Smith (ADS [illegible] 1940) showed enlargement of the liver and spleen and had 5% monocytes and 43% large lymphocytes [illegible] the blood. Ta[illegible]g (ADS 23 592, 1932) presented the case of a man [illegible] the lesion being [illegible] involvement [illegible] real, excepting the hands, feet and scalp the lesion [illegible] blotchy with pigmentation, telangiectatic macules and atrophic depigmentation.

Oliver (ADS 33 [illegible]67, 1936) presenting a patient with mycosis fungoides and atrophic lesions, reviewed the subject and distinguished 4 types of poikiloderma that of C[illegible]

that of Jacobi, the myositic, and the sclerodermatous. The case of Cormia (BJD 49: 13, 1937) seems to have been an ill-defined example of Jacobi's type. Some cases do not develop mycosis fungoides, believed Downing et al. (ADS 56: 740 1947)

A mother and her son were both affected with this rare disease, reported Hallman and Patiala (ActaD-V 31: 401 1951) Onset in a region repeatedly traumatized by refrigeration has been cited: the patient of Downing and Edelstein (ADS 62 206, 1950) carried ice occupationally on the shoulder which became affected; see Bowman and Clark (ADS 15: 583, 1937)

Poikilodermatomyositis of Petges and Cléjat differed, Tauwig said, from the disease of Jacobi solely in the presence of myositis and muscular atrophy Hottmann (AfDuS 153: 747 1927) and Jaffé (AfDuS 159: 247 1930) described under the title scleropoikiloderma cases associated with sclerodactylia and considered them variants of scleroderma. Postma and Prakken (ActaD-V 15: 373, 1934) reported a case with widespread muscular atrophy scleroderma and sclerodactylia, and they outlined the problem of interrelationship

See Jacobi (VerhandlDeutschDGesellsch, 1906, p. 321); Petges and Cléjat (AnndeD 7 850 1906; 1 441, 1930) poikilodermatomyositis Richter (AfDuS 167 222, 1933) scleropoikiloderma MacDonald (MJ&Rec. 137; 378, 1933) case; Kinnear (BJD 47: 101, 1935) classification Nékam (AnndeD 9 31, 1938) parapsoriasiform case, onset in childhood, Guy et al. (ADS 40 867 1939) poikilodermatomyositis Cannon et al. (J 118 122, 1942), atrophy following arsphenamine dermatitis resembling poikiloderma of Jacobi; Bloom (ADS 45 784, 1942), onset at age 12; Driver and Cole (ADS 48, 575, 1943) onset at age 5; Netherton and Curtis (ADS 47, 417 1943) case, Roxburgh (BJD 58 237 1946) case resembling atrophic lichen planus; MacCormac and Wigley (BJD 58 68, 1946) case Gold, Howell, Lyons (BJD 64 339 341, 1952) 3 cases, one with mycosis fungoides supervening.

AINHUM

Ainhum is a disease affecting the pedal digits. It is characterized by the development of a callused groove which constricts, strangulates and leads ultimately to spontaneous amputation within 3 to 10 years of the toe distal to the groove Cases are occasionally observed in the United States, but the disease is essentially a tropical one The vast majority of its victims are Negroes. Ulceration occasionally develops at the site of the encircling band; this results in some pain, which is otherwise inconsequential While the separation commonly occurs at the first or second phalangeal joint, it may take place in the continuity of the phalanx.

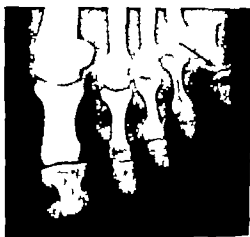
Keratoma Hereditaria Mutilans is the title applied by Vohwinkel (AfDuS 158: 354, 1929) to such cases as suffer spontaneous amputation through the effect of encircling bands in association with palmar hyperkeratosis. Four types of annular digital bands were discriminated by Wells and Robinson (ADS 66: 569 1952): congenital bands, those related to trauma, those related to ainhumlike diseases, and ainhum. Prenatal loss of two fingers from one hand was seen in the case of Neumann (ADS 68: 421 1953) who reviewed the literature on such "congenital pseudoainhum." Fingers as well as toes are sometimes attacked by encircling, amputating bands resembling ainhum; such cases were reviewed by Bluefarb (ADS 57: 741, 1948) "Lipoatrophia anularis" was the title applied to a case in which the forearm was encircled by a band of fatty atrophy seen by Ferreira Marques (AfDuS 195: 479 1953)

Etiology is uncertain. The name ainhum should not include all cases of digital amputation even if the term is limited only to amputations associated with encircling bands. Lepra, scleroderma, cicatrix, and atypical forms of keratoderma have all caused spontaneous amputation Wellman noted that the joint flexures of many Negroes, even those not affected with ainhum, are thick, rough, scaling sometimes ulcerated, particularly beneath the fifth toe He (J 46 636 1906) reviewed the theories of etiology and discarded these Zambaco Pasha's hypothesis of causation by leprosy for this is not the case da Silva Lima's belief that ainhum is due to injury for it usually affects those Negroes who wear shoes Schcubo's suggestion of trophoneurosis, for neural lesions are not demonstrable proximal to the groove Corre and Despetit's explanation on the basis of scleroderma, to which Acton (IndJMRes 15 1085 1928) later gave credence Proust's idea of congenital, intrauterine amniotic spontaneous amputations, for these are present at birth and are not limited to the phalanges and the theory of self-mutilation with rings or strings for this is not the case

Heredity does not play an etiologic role in true ainhum, and the disease is never congenital, according to Usery (AlabamaSMJ 13 319 1944) Yet fa

milial cases were reported by Weinstein (SouthMJ 6 651, 1913) and by Simon (J 76 590 1921) who saw a patient whose father and brother also suffered the loss of a toe.





Figs 1305 and 1306—Ainhum, lesion of fifth toe of Negro, and roentgenogram showing atrophy of phalanges. (Spinzig AmJRoentg 42: 246, 1939)

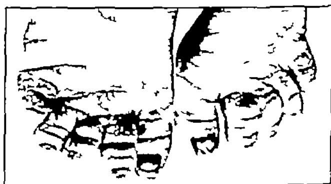


Fig. 1307—Ainhum-like lesions of toes. (Drs Kessler and Kessler)



Fig. 1308—Ainhum-like result of late syphilis. (Dr O. G Costa.)

The fathe a d mother of the patient reported by Duhring (AmJMedSci 87: 150, 1884) were affected. Stelwagon (Diseases of the Skin Saunders, 1921 p. 654) recorded an example in which the toes and fingers were i volved, and there was also present a generalized dermatosis suggestive of pityriasis rubra pilaris. A child seen by Sutton, Sr ultimately succumbed to a nervous disorder of obscure nature and a topsy disclosed de

generated areas in the cord and sclerosis and neuritis of the peripheral nerves. Wigley (BJD 41: 188, 1929) reported an extraordinary case of volar hyperkeratosis associated with ainhumlike constrictions of the fingers.



Figs. 1309 and 1310.—The great toe of the mother and the great toes of her son, 3½ years old, whose volar skin was callused and fissured. (Sutton: ADS 24: 26, 1931.)



Figs. 1311-1313.—Roentgenograms from left to right show foot of normal 3-year-old boy, foot of patient of Fig. 1310 and foot of normal 4 year-old boy. The terminal phalanx of the patient's great toe is short and deficient in its cancellous tuft.



Fig. 1314.—Keratoma hereditaria mutilans. (Dr W E Eastland.)

A boy examined by me (ADS 33: 26, 1933) whose mother was similarly affected, had abnormally short terminal phalanges of the great toes, and absence of the terminal cancellous tufts. This resulted in weight-bearing on the creases beneath the interphalangeal joints instead of on the pads of the toes, and so led to the production of grooved calluses.

The bending of a digit at the site of a grooved callus is the analogue of bending a paper tube; bending a tube occludes the hole through it. Seen 15 years later this boy's toe still would undergo fissuring if he went barefoot, but was otherwise asymptomatic.

Pathology.—There are marked hyperkeratosis and a considerable degree of acanthosis. The papillae are elongated, narrowed and densely infiltrated with small round cells. Many of the vessels show obliterative endarteritis. In the cases reported by Weinst in (JParamaCanalMA 4: 110 1911) Darling found that the constricting ring consisted of thick laminae of keratosquamous epithelium that the stratum malpighii was relatively narrow and that the corium beneath was thin and lacked papillae for the corium and the periosteum merged into one another so that they could hardly be differentiated. As the normal skin was approached, the rete increased in thickness, and its cells became larger and vesicular. The papillae also became more evident, although they were not long and filiform as they usually are in this location. At the margin of the horny ring, the corium was greatly altered by ulceration, being infiltrated by polynuclear leukocytes, red cells and fibroblasts. Many newly formed arterioles and capillaries were seen. In the tissue distal to the ring the epithelium and corium presented the usual deep filiform appearance commonly seen in the skin of this region, and the blood vessels, sweat glands, nerves and Pacinian corpuscles appeared normal. The pathologic process was explained as being mechanical after preliminary local disease produced by injury or infection had induced cutaneous fibrosis, by Bloom and Newman (ADS 27: 783, 1933). Histologic findings give no clue to the cause, thought Kean and Tucker (APath 41: 639 1946). Roentgenologic findings were described by Spinzig (AmJRoentg 42: 246 1939).

Treatment.—Transverse incisions of the constricting band in the earlier stages of the disease have been suggested by Lima (AmArchD 6 367, 1880) and others, but this measure seldom succeeds. Amputation is usually indicated. Following operation, pain disappears, and the stump generally heals promptly. Orthopedic correction may prevent the further evolution of an early case.

See Wucherer (AfPathAnat 56: 374 1872); Eyles (Lancet 2 576, 1886); Pacha (TransInternatLepConfr 2 468 1897), Moreira (MonatshPrakD 30 361, 1900) 19 cases. Brayton (J 45 87 1908) review. Yuen (AfPathAnat 290 648 1933) 13 cases, histology. Irgang and Alexander (ADS 30 602, 1934) relief of pain with L V N I. Harrower (TransRoySocTropMed 29 73 1935), trophic cause. H rowitz and Tunick (ADS 36 1058, 1937) 6 New York cases; Bennett (JMAGeorgia 27 52, 1938) case. Drummond (IrishJMSc 164: 86, 1939), band scleroderma f fingers. Montgomery (ADS 45 400 1942) 2 cases. Spencer (ADS 46 674, 1942), case associated with vola hyperkeratosis. V ughn et al (AnnSurg 122 868, 1945) 3 cases of dactylolysis spontanea. Tye (NEngJM 234 152, 1946) onset at age 77; Young (SouthMJ 41 29 1948) amputation.

SENILE ATROPHY

Senile changes in the skin usually develop slowly and consist of loss of subcutaneous fat and thinning of both dermis and epidermis. Manifestations of atrophy are seldom pronounced before the fiftieth year but they may develop early. The skin becomes yellowish thin, harsh and inelastic, and is frequently the seat of brownish or blackish pigmented macules, some of which develop into keratoses. The changes are usually most marked on exposed parts the face neck dorsa of the hands, and the legs. Occasionally the affected skin instead of being dry rough and harsh, is soft, pliable shiny and marked by whitish, atrophic spots or streaks. The hair follicles are affected and the dermal papillae are flattened. Histologically the elastic tissues show the most marked changes (Hill and Montgomery JID 3: 231 1940). Itching is a frequent symptom especially in winter when the humidity is low and the skin is dry and harsh.

Complaints can be ameliorated by the use of simple emollient applications and the avoidance of excess of sunshine hot water and soaps. Some skins tolerate cool water when hot water provokes itching.

Attention should be given to adequacy of nutrition especially of protein, while vitamin concentrates, especially the B complex, and hormones may prove helpful. Both androgen and estrogen appeared to encourage regeneration of the senile epidermis according to Goldzieher (JGerontol 4 104 1949); see Eller and Eller (ADS 59 449 1949). Many an old person needs a little thyroid as Hashinger has pointed out.

Compare Xeroderma pigmentosum (p. 12..) Werner s syndrome (p. 10..8).

See L na (Hist pathology of the Skin, Macmillan 1896 p 976). Cheatle (TMJ 1: 1412, 1909) biotripsy. Pusey (Principles and Practice of Dermatology Appleton, 1926, p. 976); Ejiri (be ADS 27 666, 1939), histologic relation with age and region, 710 biopsies of 58 cadavers. Strobel (AfDuS 186 636, 1948) lifetime tissue changes, 210 biopsies from various age groups.

KRAUROSIS

Kraurosis is a progressive sclerosing atrophy of the mucocutaneous teguments of the vulva which leads gradually to stenosis of the vaginal orifice, to disappearance of the labia minora, prepuce, and clitoris, and to effacement of the labia majora (Montgomery et al ADS 30 80 1934) It often follows recurring, infective dermatitis, according to Savill (BJD 52 321 1940) The mucosa becomes smooth, shiny and dry; the color is white waxy yellow or spotted and complication by leukoplakia is frequent so that the development of carcinoma is likely Cole (1937) told me that, in his opinion, cancer always develops if the disease continues long enough Kraurosis is not to be confused with inflammatory leukoplakia, lichen planus, lichen sclerosus, neoplastic leukoplakia, lichen simplex, or disease resulting from chronic pruritus due to contactants or parasites. Yet there is considerable similarity between vulvar lesions of kraurosis, mucosal lesions of avitaminosis A, the Plummer Vinson syndrome (q v) and lichen sclerosus (q v) the chronic, progressive, atrophic sclerotic process which often affects the vulva or the glans and prepuce of the male (Freeman and Laymon ADS 44 547 1941) Kraurosis is a shriveling disease of later life progressive and associated with severe itching as a rule

Kraurosis of the penis is described (Beck ActaD-V 19 603 1939 De Gregorio et al. AnndeD 10 588, 1939) wherein symptoms and mucosal alterations are analogous to those occurring in the female.

Etiology and Pathology—The cause is not understood fully One is on safe ground in presuming that nutritional and hormonal imbalance are importantly concerned. The underlying pathologic basis is thought to be suppression of ovarian function by senile involution, sclerosis, or castration.

Pathology—The atrophic changes involve the dermis, epidermis, and the skin glands. Halkin (AnndeD 4 65 1923) found sclerosis and degenerative changes in the elastic tissue he considered kraurosis vulvae a distinct clinical and histological entity Ketron and Ellis (SGO 61 635 1935) believed that the connective tissue changes are very similar to those occurring in white-spot disease That kraurosis is lichen planus atrophicans was urged by Hunt (BJD 48 53 1936) Adair and Davis (SGO 61 433 1935) considered the lesion precancerous. Of the 15 patients of Frigyesi (abs YBD 1937 p. 425) 3 developed carcinoma.

Diagnosis.—The confusion between kraurosis, dermatitis venenata (textile soap medicinal) mycotic vulvovaginitis, lichen simplex lichen planus, tinea, leukoplakia (a symptom not a diagnosis) and superficial carcinoma is not to be dispelled by the written word. One must see these different diseases with a competent teacher Clarification of the differential diagnostic features of kraurosis (primary atrophy) neoplastic leukoplakia, senile atrophy and lichen sclerosus was presented, with color plates, by Wallace and Whimster (BJD 63 241 1951) Careful consideration and examination of each case with these possibilities in mind, combined with the prescription of intelligently appropriate remedies for whatever is present in that case and with due disregard of statistical assemblages of dissimilar examples—these measures will clarify instruct and, even, occasionally cure

Treatment.—Some authors, recognizing the condition as precancerous, advise vulvectomy at an early stage Vulvectomy generally becomes necessary (Sparrow: AnnSurg 112 87 1940) although many reports of the efficiency of estrogenic hormonal substances have given encouragement in this distressing disease (Foss: JObGyn 46 271 1939 Buxton and Engle J 113 2318 1939)

Estrogen may help the atrophy without relieving the itching so that resort to surgery may still be required. Stilbestrol, 20 mg to the ounce of petrolatum applied locally apparently cured a patient of Feldman (ADS 43 756 1941) Estrogen in suitable dosage when given intramuscularly may yield greater benefit than when given by mouth or applied locally Hydrochloric acid vitamin B complex and iron may be given by mouth. Administration of vitamin A and if hypochlorhydria is present, HCl may be helpful (Swift JObGyn 43

1053 1936) Cortisone by mouth and hydrocortisone ointment are sometimes of excellent effect. Roentgen therapy may afford temporary relief. Bland antipruritic lotions and packs may be used. The avoidance of contactant irritants is advised.

See Breisky (Ztschr f Heilk, 1885, p. 69) original description Ohmann-Dumesnil (New OrlM&SJ 17: 283, 1890) Baldy and Williams (AmJMedSci 128: 828, 1899) Delbet (BrugesChir 38 809 1924) kraurosis and cancer Sulzberger (inaugural dissertation, Zurich, 1924) Fabry (DWchn 80 7 1928) penile Taussig (AmJObGyn 18 472, 1929) Davis (SGO 61 680 1935) estrogen treatment of senile vaginitis; Jacoby and Rabbiner (AmJObGyn 31: 681, 1936), estrogen in senile vaginitis Bishop (BMJ 1: 619, 1937) estrogen helpful in senile vaginitis Ellis (ADS 39 906, 1939) histology, Jeffcoate (BMJ 2 672, 1939), estrogen helps vulvar pruritus only in cases of estrogen deficiency Finkler and Antopol (Endocrinol 25 925, 1939), senile vaginitis benefited by oral estrogen Saville (BJD 52: 338, 1940) Hesseltine (AmJObGyn 42 702, 1941) vitamin therapy Madden (ADS 47 671, 1943), diethylstilbestrol suppositories Klaften (JClinEndocrin 3 712, 1943), estrogen ointment helped 7/9 of 68 cases of pruritus Hunt (Diseases Affecting the Vulva, ed. 4 Mosby 1954)

DYSPHAGIA AND XEROSTOMIA IN WOMEN
PATERSON KELLY PLUMMER-VINSON-SJÖGREN SYNDROME

Dysphagia, glossitis, hypochrome anemia and achlorhydria are classic features of a disorder which occurs in middle-aged and older women "The lips are thin and the opening of the mouth is small and inelastic" wrote Andrews (Diseases of the Skin Saunders, 1946) and "Atrophy is most pronounced on the tongue which in typical cases is entirely smooth, but there are associated atrophic changes in the mucosa of the mouth pharynx and esophagus. Inflammation is also present the lips may be swollen and crusted, and the tongue enlarged, tender and bright red"

Dysphagia in this condition may resemble hysteria and it was to hysterical malnutrition that Vinson (MinnM 5 107 1922) attributed the condition, malnutrition being he thought the cause of the organic disease In his review of 69 Mayo Clinic cases, he made no mention of spoon nails or oropharyngeal cancer The dysphagia becomes localized at the level of the larynx, according to Gerlings (JLaryng 55 143 1940) who observed on fluoroscopy stagnation of barium in pharyngeal pockets above the laryngeal aditus. The mucosa is thin and may even be ulcerated (Kernan AOtol 32 662 1940) Hyperkeratosis and atrophy affecting the pharyngeal and esophageal mucosa are suggestive of nutritional and hormonal deficiencies.

Xerostoma may progress to hyperkeratosis and this to leukoplakia and perhaps squamous cell carcinoma and when cancer of the pharynx or esophagus does occur in women it is commonly the result of this syndrome according to Ahlbom (BMJ 2 331 1936) The cheilitis suggested ariboflavinosis to Franceschetti (abs J 122 713 1943) Dysphagia weakness, brittle nails, and iron depletion were accurately described by Dameshek (J 100 540 1940) Koilonychia is a usual feature (Anderson ADS 37 816 1938)

Keratoconjunctivitis sicca with filiform keratitis accompanied by xerostomia, rhinitis sicca, pharyngitis and laryngitis, was the contribution of Sjögren (ActaOphth Supp #2 1933 #13 1935 #16 1938) The lacrimal and salivary glands may also partake of the atrophy which is accompanied by chronic inflammation (Latman and Favata: AOphth 35: 227 1946 Ellman et al. QuartJM 20 33 1951) and recurrent swellings (Morgan and Raven (BritJSurg 40 154, 1952) Secondary cough, achlorhydria, dry skin, dry vagina with mucosal atrophy low blood pressure low blood calcium accelerated sedimentation rate acrocyanosis, telangiectases of lips and fingertips, sclerotic changes of the skin of the legs, and mental abberations were noted by Weber (BritJOphth 29: 299 1945) and Ellman and Weber (BMJ 1 304 1949) although eye lesions are often absent from cases which fall within the broad category

Priority of description is difficult to establish. Paterson (BMJ 1 252, 1906) described a case which had progressed to carcinoma affecting the epiglottis. Studies by Paterson (BritJLaryng 34 283 1919) and by Kelly (ib., p. 289) were the early reports found by Morrison et al. (RevGastroenterol 8 19 1930) who were concerned with a syndrome of hypochrome anemia, achlorhydria and atrophic gastritis. "Paterson's syndrome" was the title preferred by Hurst (BMJ 1: 1201 1930)

Pernicious anemia was present in [illegible] patients of v Gross (KlinWchn 15: 318, 1909) Increased fragility of the red blood cell was found by Graham and Johnson (QuartJM 1 41 1932) who therefore distinguished the anemia from the ordinary secondary sort.

Pathology.—The changes are epidermal. The horny layer is thickened without apparent parakeratosis, the prickle layer is thinned, and the stratum granulosum absent. The papillae are narrow and elongated *(alpine papillae)* and the basal cells of the epidermis are flatter and less regularly arranged than normal. Hyperkeratosis tends to occlude the orifices of the sebaceous and coil glands, but is insufficient in degree to give rise to papule formation. The sweat ducts and acini are usually dilated, and the sebaceous glands atrophic.

Treatment.—Hydrochloric acid, iron, and vitamin concentrates, especially B complex and vitamin A appear indicated, while esophageal dilation may be required. The mechanical as well as the nutritional qualities of the ingesta must be considered. Since vulvar changes in kraurosis resemble those of the pharynx in this syndrome estrogen in suitable dosage might help Androgen by peroral absorption cured the patient of Brückner (abs J 130 978 1946) ACTH was palliative in the patient of Frenkel et al. (abs J 6 161 1951) Vitamin A appeared curative in the case of Stahel (KlinWehn 17 1692, 1938) although this was of no benefit in the case of Allington (ADS 60 1050 1949) Iron therapy was curative in a patient of Savilahti (ActaMScand 125 40 1946) who attributed dysphagia to muscular degeneration in the esophagus. Iron therapy must be repeated twice a year for it produces no permanent improvement and hypoproteinemia is a result of the disease believed Bingham and Locan (BMJ 2 650 1953) No success was obtained with vitamin B preparations given by Lutman and Favata (AOphth 35 227 1946) Favorable response in Sjogren's syndrome was obtained by giving 5 gtts t.i.d. of 2% pilocarpine P O and injections of estrogens and B_{12} in the case of Kenny and Long (J 155 435 1954) Finding that stellate pericarotid infiltrations with procaine gave temporary relief, sympathectomy of the intermediate cervical ganglia was performed by Leriche (PresseM 55 77 1947) with disappearance of the dryness of the eyes and mouth.

See Moersch and Connor (AOtol 4 112, 1926) 63 Mayo cases, Hurst (J 102 582, 1934); Hoover (NEngJM 213, 394 1935) koilonychia with anemia, glossitis and dysphagia; Anderson (ADS 37 816, 1938); Sheldon (BJD 51 60, 1939), Sjögren syndrome accompanied by pigmentation and scleroderma of the legs; Degos et al. (ReocfrancD Jan., 1939), benefit with vitamin C Weber (MPract 212 283, 1945), review; Coverdale (BritJOphth 32 669, 1948) familial cases; Klein (Brit JOphth 33 387 1949), studies of cornea; Behrman and Lee (ADS 61 63, 1950) case and review Raffle (BMJ 1 1470, 1950) case Touraine (PresseM 58 408, 1950) 101 cases of "Gougerot Houwers-Sjögren syndrome"; Cooperman (AnnWestMAS 4 344, 1950) "Sjögren secreto-inhibitor syndrome"; Harrington and Dewar (BMJ 1 1302, 1951), case affecting male with pigmentation and scleroderma of legs; Gurling (AnnRheumatDis 12 212, 1953) association of Sjögren and Felty syndromes in 2 cases, and relation to rheumatoid arthritis; Gurling et al. (BritJOphth 38 619 1954) ACTH no help in Sjögren syndrome, 6 cases.

MALFORMATIONS AND NEOPLASMS OF THE SKIN AND ADJOINING MUCOSAE

DISTURBANCES OF GROWTH

Disturbances of growth characterize neoplasm the subject of this chapter Embryology appears to be the key to these Aberrations of cell form and tissue function comprise the benign and malignant tumors, which may be interpreted as manifestations of one process. The modern concepts of abnormality of organization, induction and genetics represent clarifications of ideas held by wise old observers such as Cohnheim, who spoke of versprengte Keime (sprung up embryos) and Albrecht who coined hamartoma (error tumor) See Harvey (EdinMJ 55 1 1948) The range of variation among *tumors seems almost endless but appears to be governed* by the number and variety of tissues involved in the anomaly and the genetic or mutational potentialities of the cells of which they are composed Abnormalities may be localized or systematized in distribution Some varieties are common while others are rare and still others almost unique

ICHTHYOSIS

Synonyms.—Fish-skin disease Alligator-skin disease Xeroderma Xerosis Sauriasis Congenital hyperkeratosis.

Symptoms.—Ichthyosis is characterized by epidermal abnormality with dryness, harshness scaliness and other manifestations of irregular hypercornification It is a fairly common condition. The disorder is usually solely cutaneous and ranges considerably in distribution and degree of severity The general health is unaffected. Extensor surfaces of the limbs are the sites of predilection although the entire body may be involved. During warm months when the skin is moist and better lubricated, the lesions in mild cases are scarcely perceptible but the disorder becomes conspicuous in the low humidity and cold of winter Some patients, lacking the ability to perspire carry a slight fever in the summer (Thannhauser J 106 908 1936) and their fatigability and tremor simulate hyperthyroidism They are especially vulnerable to irritation by soap and to pruritus induced by dryness. The face escapes involvement except in severe cases, which may show parched scaliness, tautness, eyelid changes and ectropion with glazing of the conjunctiva and danger to the cornea (Cordes and Hogan AOphth 22 590 1939) but it is rare for the cornea to be affected by participation in the epidermal defect (Vail AOphth 24 215 1940)

The various congenital polykeratoses were classified by Touraine (BullD 66 294 1954) including the cutaneous, follicular subungual and mucocutaneous varieties.

CONGENITAL ICHTHYOSIS when present is noticeable at birth or shortly afterward as a rule In the more pronounced examples thickening roughness and scaliness are exaggerated and the hair of scalp and eyebrows becomes dry and loses its luster and becomes somewhat sparse As a result of lessened elasticity and flexibility fissures may develop in the natural folds of the affected areas of the skin. In some instances the skin is extraordinarily susceptible to the effects of even slight irritation, ichthyosis irritable of Besnier Both the sebaceous and coil gland secretions are deficient The involvement is more pronounced on the areas where the skin is normally thick and stationary The axillary antecubital and popliteal areas largely escape

The disease appeared ... 3 ... molers ... f a f mil not previously affected (BB ... 62 ... 1931) In a ... b l l w th ge ... ralized i hth osl ... whi h w ... th fam ... number of maternal ... b ... h d k ratosis palmaris et pl ... although thel ... otherwise apparently normal (H rman ... DWeb 1 4 100 1931)

Fig. 1315.—Ichthyosis onset at the age of puberty limited to trunk and arms; lower extremities were normal. (Drs. Morrow, Miller and Taussig.)





Figs. 1316 and 1317.—Ichthyosis. (Dr. George Lingenfelter.)

HARLEQUIN FETUS.—The condition may be grievous at the time of birth to such a degree that the infant is most pitiable. The majority of such victims die either at birth or shortly afterward (Shields and Bowman: APed 57: 756 1940). In a case under Sutton Sr s care the skin was so lacking in suppleness and elasticity that fissures developed on the trunk and at the buccal commissures as a result of even moderate movement, and up to the end of its first year the child was at no time free from lesions of this character. Ectropion, puckering of the mouth and *distortion of the ears likewise were* present. The skin on the body was smooth dry and hard, and the color of flexible collodion. Kingery (ADS 13: 90 1926) reported an extraordinary example. Wakeley and



Fig 1318 —Ichthyosis, showing ectropion.



Fig. 1319 —Ichthyosis.

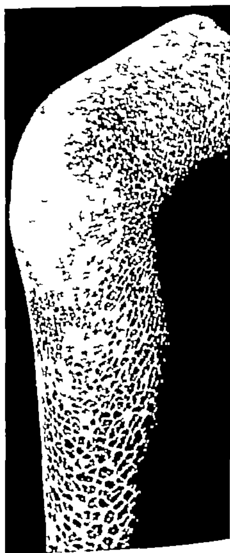


Fig. 1320 —Ichthyosis. (Drs. H. C. Sweeney and J. H. Hallwig.)

Thomson (JObGyn 28: 190 19?1) have studied the subject and Ingman (ActaD-V 5: 125 1924) reviewed ichthyosis congenita in relation to syphilis which i coincidental when present. Deformity of such extreme degree as to render the f tuses n viable occurred in 2 consecutive pregnancies, reported by D'Oelsnitz et al. (Pédiatrie 7: 11-3, 19?.).

Symptomatic Ichthyosiform Change (Xerosis) is seen in pellagra, avitaminosis A dehydration chronic debilitating disease and the like (Jeghers NEngJM 228 714 1943). A patient with lymphosarcoma and hepatic insufficiency exhibited acquired ichthyosis (*Glazebrook* and Tomaszewski ADS 55 28 1947)

ACQUIRED ICHTHYOSIS is relatively rare but cases do occur (Crocker Diseases of the Skin, Blakiston, 1 562, 1908) Crocker stated that the *Piper methysticum* chewers of the Sandwich Islands oftentimes develop the condition. Its occurrence has been noted in tabetics. Acquired ichthyosis requires evaluation of liver function and protein, estrogen thyroid and vitamin A metabolism. Its spontaneous appearance sometimes signifies an early stage of Hodgkin s disease (Welch and Epstein J 148 1221 1952)

ICHTHYOSIS FOLLICULARIS is the name applicable to congenital ectodermal defect with follicular spines. It was described by Macleod (BJD 21: 165 1909) in recording 3 cases resembling keratosis pilaris, q.v See Manson (BJD 33: 20 1921)

DECIDUOUS SKIN reviewed by Bechet (ADS 37: 266, 1938) i characterized by the continuous, periodic or seasonal shedd ng or peeling of the epidermal layer of the skin of more o less general distribution (see p. 835) The palm do not scale. The shedding continues throughout life. This is probably form of congenital ichthyosiform disease.



Fig. 1331.—Ichthyosis, dark because of thick ker tinization. Note freedom of flexures. (Dr Robert N Andrade.)

Lamellar exfoliation of the newborn was described by Shelmire (AD 71: 471 1955) a rare peculiar self-limited disorde wherein the infant is completely env loped in a constricting membrane resembling collodion or oiled parchment. He ascribed priority f description to Bowen (JCutD 14 485, 1896) Premat rity is an associated feature, wrote Sh lmire and constriction of the membrane produces temporary ectropion ecla bium, deformit of the ext rnal ears, and immobility nd edema of the extrem ties, plus pressure ischemia. A process f fissuring and peeling of the membrane usually begins within the first 4 hours, and large keratin lamellae are cast off, coincident with rapid mprovement of the general well being of the infant. The skin heals and becomes normal, the process being complete within from 3 to 10 weeks. Scott and Stone (BJD 67: 159 1955) noted th t a case was described by Fox (JCutD : 9 , 1884) and stated that the skin t birth is deep red d smooth a if varnished The distribution was limited to the head and feet in the case of Finlay and Bound (ArchDisChild 27 435, 1952) *Scott* nd Stone reviewed several record f familial involvement, i cluding the 2 brothers reported by Nicolas and Moutot (BoemAdHôpLyon 11: 501, 112) who developed severe ichthyosiform erythroderma when they reached dolescent age, as in patients described by M cKee and Rosen (JCutD 35: 233 1917)

Etiology of Ichthyosis.—The disorder is usually a congenital one. A hereditary tendency has been repeatedly noted. In the acquired cases, hypothyroidism and various conditions such as hypoproteinemia or estrogen or androgen deficiency possibly play a part. Talbot and Hendry (AmJDisChild

29 770 1925) made an interesting study of the basal metabolism of ichthyotic children Porter (BJD 38 475 1926) found that 70% of cases among children and 25% in adults showed subnormal BMR's and concluded that hypothyroidism must be present in a large proportion of instances. He thought ichthyosis may be conditioned upon hypothyroidism in the mother of the



Fig. 1322.—Ichthyosis congenita, severe.
Fig. 1323.—Ichthyosis: hyperkeratosis, acanthosis and [illegible] dermal papillae. [illegible] inflammation.



Fig. 1324.—Harlequin fetus (Dr C. P. G. Wakeley)

affected infant It is standardly my experience that thyroid medication accomplishes no good in true ichthyosis, although Kingery (ADS 13 90 1926) found changes in the thyroid and suprarenal glands in a case examined post mortem. While these cases resemble avitaminosis A and myxedema, they are not responsive to vitamin A or thyroid reported Peck et al. (AJS 4 32, 1943)

Inheritance is variable being sometimes a simple dominant sometimes a sex linked recessive (Davies and McGregor: BJD 54 121, 1942); or the disorder may appear as a mutation. See Gates (Human Genetics Macmillan 1946 vol. 1 p 313) Dominance is commoner and is frequently seen in northern European stock Recessive inheritance is said to occur mainly in Latin and Japanese persons (QMN J 153 775, 1953)

Treatment.—Frequent inunction with a bland ointment, such as cocoa butter or benzoinated lard, is somewhat comforting One per cent salicylic acid may be added to advantage These applications act best when applied immediately following a hot bath in soft water Gordon (ADS 52 178 1945) reported benefit by the use of daily baths in 3% NaCl followed by inunctions of 10% NaCl in hydrous wool fat adopting the ideas of Ljungström (ActaM Scand 108 98 1941) He gave also vitamin A, as recommended by Rapaport et al. (JPediat 21 733 1942) and, to enhance its utilization bile salts and neostigmine. No illusions should be entertained regarding the value of drug store shelves some items of which are almost certain to irritate The patient has to learn to live with his defective skin

CONGENITAL ICHTHYOSIFORM ERYTHRODERMA

This is a variety of ectodermal defect in which the skin is thickened and presents a shiny reddened, varnished appearance with a tendency to lichenification in the vicinity of the larger joints. *Erythroderma and keratosis are* variable in severity and extent but the axillae cubital and popliteal areas, least affected in ichthyosis, are most affected here (Laymon and Murphy ADS 57 615 1948) This particular type of malformation was separated as an entity by Brocq (AnndeD 33 131 1902) and a complete review was given by MacKee and Rosen (JCutD 35 235 343 511 1917) who divided congenital keratodermas among ichthyosis, keratoderma follicularis, ichthyosiform erythroderma keratoderma palmaris et plantaris, and the hyperkeratotic and verrucose nevi. See regarding symptoms and histology of the congenital dyskeratoses, the essay of Brünauer (DZtschr 42 6 1924)

Congenital ichthyosiform erythroderma in the majority of cases is present at birth or develops a few days thereafter (MacKee and Rosen) Heredity does not appear to play an important role It is about equally common in both sexes. It may begin with more or less generalized erythroderma which may be marked or inconspicuous, but thickening of the horny layer may precede erythema. As the patient grows older the reddened skin becomes thickened and scaly While erythroderma is likely to fade gradually the ichthyotic skin remains in adult life although it too may undergo some improvement. The appearance of the horny layer varies in different individuals and in various parts of the body it resembles ordinary ichthyosis, but the flexures are involved often maximally while these areas are usually spared in ichthyosis. The palms and soles may or may not be affected. The face is usually red and slightly scaly and ectropion may be present. The scalp is generally seborrheic. The hair may be excessive scant or normal

Two types of the disease are recognized, the dry and the bullous. In the latter bullae appear in frequent outbreaks, generally on the extremities, are usually flaccid and heal soon, without scarring as a rule. They are more likely to occur during winter months and become less frequent as the patient matures, so that the adult may be free of them There are periods of exacerbation and remission, improvement generally occurring during the summer

The disease is usually generalized and symmetrical but circumscribed and asymmetrical cases have been described The margins of the lesions may or may not be sharply circumscribed Perspiration over the general surface is conspicuously diminished although hyperhidrosis may be seen in the flexures and on the palms and soles The general health is unimpaired although itching is sometimes considerable

I[illegible] interesting case of congenital ichthyosis reported by B[illegible] (JCutD 33: 235, 1913) the affection bore a marked resemblance to cases described in Brocq, but in [illegible]

dition there was present buccal and nasal involvement, and the eyes and ears also were affected. Wile (ADS 10 437 1924) described 3 extraordinary cases of postnatal exfoliation. The parents of the affected children were * brothers who had married sisters, the parents being first cousins. There were 4 children in the affected family of whom only 1 girl escaped. He discussed the relationship with epidermolysis bullosa.

The remarkable fact of improvement brought about in 1 patient by hypnotic treatment was presented by Mason (BMJ : 422, 1952 BJD 64: 26, 1952.)

Keratosis Rubra Figurata.—Hyperkeratotic erythroderma in plaques with hyperpigmented borders may occur in a limited but symmetric distribution. The dorsa of the feet, legs, and thighs were affected in the boy seen by Coles (BJD 66 225, 1954) but the palms and soles were normal. The child s father had ordinary tylosis. While the outlines of the plaques are generally fixed (Gans and Kochs: Hautartz 2 339 1951) the lesions exhibited changes of configuration in the mother and daughter showing this type of epidermal change reported as erythrokeratodermia variabilis by Mendes da Costa (Acta D-V 6: 255 1925)

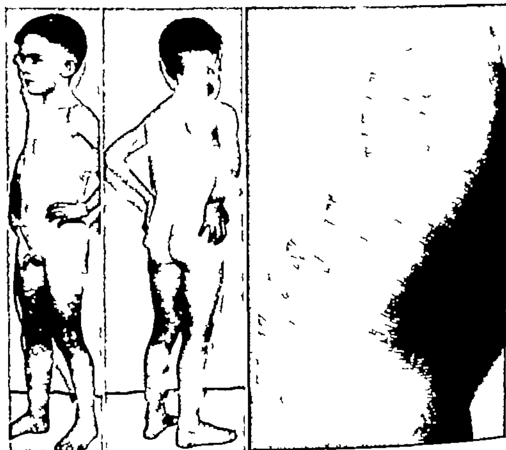


Fig 1335—Keratosis rubra figurata. (Coles BJD 66 225, 1954.)

Erythema Palmare Hereditarium (Red Palms) was the name gi en by Lane (ADS 20 445 1929) to a curious and rare redness of the palms, seen in 2 patients, bearing a relation to keratosis palmaris analogous to that between ichthyosi and ichthyosiform erythroderma. Aside from the colo comparable with that of a baboon s buttocks, the condition was without symptoms. See Erythema of the palms.

See Kurihara (ActaD-V 27 108, 1936), case Rostenberg (ADS 42: 934, 1940), case, Lawless (ADS 44 30 1941) case, Senea et al (ADS 58 534, 1948) case followed for 16 years; Fitzgerald and Rooker (ADS 64 611, 1951) 2 children in 1 family, with an atopy, Vukas (ADS 64 36, 1951), case, Barker and Sachs (ADS 67 443, 1953) bullous cases made worse by ACTH Polano et al. (PresseM 61 276, 1953) familial dominant case.

ICHTHYOSIS HYSTRIX

Ichthyosis hystrix is a peculiar type of giant nevus which may involve large areas of the trunk and limbs. It is characterized by horny hypertrophic papillary elevations in curious lineal arrangement. Warty projections range

considerably in diameter and length; in extreme cases they may impart a porcupine-like appearance The skin is dry the nails are friable and the hair is dry and lusterless. The face palms and soles are occasionally spared. Symptoms are usually absent. Ichthyosis hystrix of limited distribution is relatively common, and is frequently reported under such names as nevus verrucosus and nevus unius lateris.

Linear nevi (q v) of this sort are sometimes extremely pruritic and recalcitrant to palliation. The skin blistered easily in the unusual case of Reyes (ADS 52 328 1945) McGlasson (TexasSJM 17 255 1921 22) reported 2 instances of onychogryposis, ichthyosis hystrix and keratosis occurring in the same family Many cases of systematized linear nevi of bizarre appearance and considerable clinical interest have been recorded. The lesions may be atrophic in large part, as in the case of Liebermann (ActaD-V 16 476, 1935)

Ichthyosis is not sharply demarcated is symmetrically distributed, avoids the axillary and antecubital flexures, is not verrucose, and is characterized by polyangular plates of smooth hyperkeratosis (Bedghet BsocfrancD 41: 710 1934) In contrast, ichthyosis hystrix is a verrucose systematized nevus (Unna Histopathology Macmillan, 1896 p. 332)





Fig 1326 —Ichthyosis hystrix.
Fig. 1327 —Unilateral ichthyosis hystrix, a nevus unius lateris.

Pathology—There is enormous papillary hypertrophy with accompanying increase in size of the intrapapillary vessels. The prickle layer is comparatively thin throughout the affected areas. In consequence the hyperplastic stratum corneum dips down into the interpapillary depressions, giving rise to the peculiar spinous projections which are so characteristic of the condition. The governing factor in the distribution of the linear cases is undecided. Montgomery (JCutD 19 455 1901) concluded that the streaks probably are aligned with streams or trends of growth of the tissues and to the adaptation of the embryonic sutures.

Treatment.— As a rule nothing can be done In lesions of small extent, excision is feasible with the substitution of a neat surgical scar for a fillet of unsightly warty abnormality Local patches may be blistered off with the actual cautery at the same time destroying the vascular papillae to a uniform level, and the cosmetic result is favorable.

Ichthyosis Hystrix of Mucous Membranes.—Ichthyosiform nevoid keratosis of the mucosae of the oral cavity and other orifices has been observed. Keratosis tonsillaris the name often applied by otolaryngologist (Gilbert: MinnMWchr 69: 421 1922; Siebenman : AfLary gol 20: 101 1907) Laryngeal involvement interfered with phona





Fig 1328—Ichthyosis hystrix an extensive case. (Dr Howard Fox)

Fig 1329—Porcupine man, an example of congenital, papillomatous, ichthyosiform ectodermal defect (Dr Charles C Dennie)



Fig. 1330.—Congenital ichthyosiform defect, "porcupine man." (Dr Ralph Major)

tion in 3 members of the family reported by Miescher (DMtschr 44: 189 1925) The disorder was unilateral in the mouth of the patient of Barber (BJD 46: 280, 1934) Naevus spongiosus albus mucosa was the title of Cannon (ADS 31 365 1935) for the disorder as it affected oral, rectal and genital mucosa of a woman, her 2 sisters, her brother and her son.

Porcupine Man. —Rare indeed are cases with papular hyperkeratoses surmounting the areas of ectodermal abnormality (Bett BJD 64 59, 195_) The brownish or blackish keratoses are fitted together side by side and have rounded burnished tops. They may be picked off but form again. Fermentation of epithelial déb is renders the condition a malodorous and revolting one. The disorder was limited to the mammary regions of a girl reported by Halter (AfDuS 176: 659 1938) The case reported by Preininger (AfDuS 176 109 1937) was a man in whose excessive corneum *Ustilago maydis* grew

The family history of the original porcupine man, first described by the astronomer Machl (PhilosophTransRoySoc 3 299 1731) was traced by McFarland (ADS 22 307 1930), who found 10 patients, all males, in 4 generations. The original patient, Edward Lambert, had an affected son, and his sons, John and Richard, were also affected and were widely studied and exhibited (Marmelzat ADS 58: 349 1948)

KERATOSIS PALMARIS ET PLANTARIS HEREDITARIA

Synonyms.—Ichthyosis palmaris et plantaris Keratoderma palmare et plantare Tylosis.

Symptoms.—In this ectodermal anomaly the volar tissues are diffusely and symmetrically thickened and hyperkeratotic. Surface markings are intensified because of the relative inflexibility of the intervening skin. All degrees of severity of involvement are met with from slight roughness to great thickening The color of the superabundant horny material is yellow or brown, and the surface is usually dry and burnished. At the margins, transition into normal skin is abrupt Painful fissures are complications to which the affected skin is mechanically predisposed. The abnormality is usually recognizable at an early age It is usually inherited as a dominant Aberrant and disseminated forms of the disease are seen (Michael ADS 27 78 1933) Sometimes it is associated with ichthyosis or with congenital ectodermal defect (q v) but commonly it exists alone

That form of the disease which involves the entire volar surfaces uniformly is usually hereditary In the report by Chung (ADS 36 303 1937) of 2 Chinese families, with, respectively 3 cases in 6 generations and 19 cases in 7 generations, it behaved as a simple dominant. Michael (ADS 21 215 1933) published some interesting genetic charts corroborating this view and, finding familial and nonfamilial cases indistinguishable except the genotypes, he suggested that nonfamilial cases represent mutants. Simple Mendelian dominance occurred in the family studied by Macaulay (BMJ 1 334 1951)

Volar lesions associated with circumoral and circumanal hyperkeratoses were observed in an Italian child by Olmstead (AmJDisChild 33 757 1927) Sutton 8 saw such a case in an Italian boy Unusual tenderness and a tendency to the formation of bullae were noted in the hereditary case of Andersen (BJD 63: 177 1951) In the family reported by Everall (BJD 66 54 1954) 3 cases manifested bullae first and tylosis subsequently suggesting some relation with epidermolysis bullosa simplex. See also Pachyonychia, and Epidermolysis bullosa, localized.

Compare Keratoderma climactericum. Endocrine deficiency with volar hyperkeratosis as a symptom must be recognized as fundamentally different from the hereditable malformation under discussion. Hypothyroidism caused painful fissuring, thick volar epidermal disease curable by the administration of thyroid tract (Mouzo-Fournier BullméSocméd 48 1236, 1932; Cervino et al.: Endocrinol 22 615, 1938) A drogenic substances greatly benefited a senile patient of Henschen (SchweizMWch 0: 690 1940) and seemed to help a child treated by de Rezende (abs YBD 1930 p. 68)

Treatment.—No cure exists for the malformation which must be lived with as can best be managed In treatment a bland base with from 1 to 5% salicylic acid incorporated in it may prove comforting Prolonged poulticing with hypertonic sodium chloride solution gives some comfort If the patient can avoid manual labor he will be less prone to extreme hyperkeratosis and fissuring Careful paring with a razor blade may be tried. Porter (BJD 63 123 1951) claimed benefit in 3 of 6 patients to whom he gave generous

doses of vitamin A. The extreme severity of the disease in a woman reported by Dencer (BritJPlasticSurg 6 130, 1953) justified excision of the soles and grafting a surgical endeavor which proved satisfactory

Disseminated Forms of Palmar and Plantar Keratosis exist and have received considerable attention. Lesions may occur in patches or nodules, in striated or in punctate configuration. Symmetrically located disseminated, macular lesions which were not familial were described by Buschke and





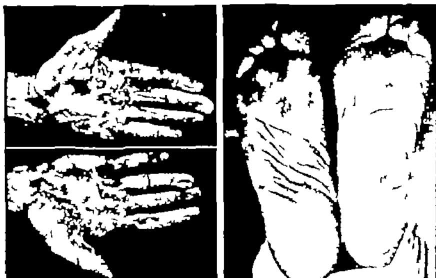
Fig 1331 —Keratosis palmaris, hereditary (Drs Muller and T...)
Fig. 1332 —Keratosis palmaris hereditary histologic structure





Fig. 1333 —Keratosis palmaris et plantaris, extreme. (Dr Robert N. Andrade)
Fig 1334 —*Keratosis palmaris et plantaris disseminatum* (Dr Gusta Riehl)

Fischer (IkonogDermat 5 183 1910) while similar lesions, 8 examples being found in 1 family were described by Brauer (AfDuS 114 211 1919) The 33 cases among 65 members in 5 generations of a family observed by Michael (ADS 21 215 1933) were of the hereditary type Striated forms represent either part of the manifestations of a case of ichthyosis hystrix or *formes frustes* thereof The palms or soles or both may be involved and involvement may be unilateral The congenital keratodermas were extensively reviewed by



Figs. 1335 and 1336.—Keratosis palmaris et plantaris, striate form.



Figs. 1337 and 1338.—Keratosis palmaris et plantaris, punctate form.



Fig. 1339.—Keratosis punctata. (Dr. O. G. Costa.)

MacKee and Rosen (JCutD 35 235 343 511 1917) Warty lesions were present in the consanguineous husband and wife reported by Galloway and Adamson (BJD 30 123 1918)

Compare arsenical keratoses. See Petracek (ActaD-V 16 38, 1935), 6 cases Buschke-Fischer type; Nicholas et al. (BsocfrancD 43: 921 1936) nodular, familial Senmes (ADuS 137 392, 1929) striat dominant Jacobson nd Anderson (ADS 47 766, 1943) unusual, limited to soles Hanhart (Dermatologica 94 286, 1947), disseminated, 11 cases in 4 generations, associated with lipomas Orzybon ki (AnndeD 8 378, 1948) linear ichthyosiform nevus of left hand, Nessmead (Dermatologica 99 187 1949) 10 cases in 4 generations Hal (BMJ 1: 941 1950) remarkable child.





Fig. 1340.—Keratosis punctata of palm (biopsy wound on the thenar eminence)
Fig 1341 —Keratosis punctata, from a lesion of the foot. (Dr Sam Switzer)





Figs. 1342 and 1343.—M J de M leda I an Italian American residing in Kansas City M

Keratosis Punctata (Keratoderma Punctatum) was described by Hallopeau and Claisse (BsocfrancD 2 116 1891) as a peculiar keratosis of the palms and soles characterized by the occurrence of numerous, minute crateriform pits set in patchy thickening of the corneous layer It is a form of disseminated keratosis palmaris Neither sex is exempt and the disease may occur at any age (Chalmers JTropM 20 121 1917)

The cause i unknown. Hallopeau and Clai se believed it to be a form of nevus Many cases have bee described ince theirs. The patient of Sutton Sr was a man 43

years old, whose lesions had developed after puberty. Lieberthal (ADS 14: 655 1926) reported an example in a man 53 years old, whose lesions had been present on the hands and feet for 16 years.

Matsumoto (JCutD 36: 290 1918) reported a case and distinguished 3 forms of disseminated volar keratoderma: (1) peripherally extending keratoderma of the palms and backs of the hands, the type of Vorner (AfDuS, 1911, p. 161); (2) Buschke and Fischer's horny volar nodules with pitted centers; and (3) Brauer's hereditary type with circular clavuslike or wartlike papules.

The case of Semon (ProcRoySocM 22: 340 1929) was unilateral and had its onset in adult life. I have seen a similar pitted keratoderma limited to one palm. The case of White (JCutRev 34: 394, 1920) was a peculiar pitted type keratosis of the palms and soles which had its onset after the patient was 30 years old.

Punctate hollows may occur on the palms with or without keratosis palmaris, according to Baker (AnndeD 6: 225 1923). The disorder was found in a man with bronze diabetes by Sims (ADS 26: 635, 1933). The lesions, suggestive of some kind of warts, had been present only 3 months in the man observed by Phillips (BMJ : 689 1947). Three cases of the rare disorder were studied by Scott et al. (ADS 64: 301 1951). See Galloway (BJD 30: 123, 1918); Sweitzer (ADS 8: 637 1923).

Mal de Meleda is a hereditary ectodermal defect resembling keratosis palmaris et plantaris, with involvement of the dorsa of the hands and feet and extension onto the forearms, elbows and legs, in association with dystrophy of the nails. Kogoj (ActaD-V 15: 264 1934) described 9 cases from the Isle of Mljet where it occurs, and suggested the name keratosis extremitatum hereditaria progrediens. The inheritance is recessive, so the frequency of its incidence must be due to inbreeding (Bošnjaković ActaD-V 19: 88, 1938). The distinctive features are tylotic thickening of the volar skin, ichthyosiform thickening of the skin elsewhere, delimitation of involved from uninvolved skin by undulating geographic lines, and absence of desquamation, the skin being moist and normally oily (Photinos and Souvatzides BsocfrançD 46: 177 1939). One of the 4 cases of Niles and Klumpp (ADS 39: 409 1939) seemed to have been helped by x-ray therapy. A case was reported by Brunner and Fuhrman (ADS 61: 820 1950). Occurrence in 2 sisters and in a woman and her 3 brothers was noted by Greither (Hautarzt 5: 447 1954).

Atypical Volar Hyperkeratoses.—Curious cases were reported by Gasser (abs BJD 62: 472, 1950). Horny wartlike lesions forming plugs that penetrated into the skin were seen on the palms in a patient of Arnold (ADS 55: 633 1947). Sharply circumscribed, red, finely scaling lesions were disposed transversely in areas on the backs of the hands and feet and elsewhere, with volar hyperkeratosis also, in the remarkable case of Melczer (DWehn 108: 65 1939).

Keratoma hereditaria mutilans was the title applied by Vohwinkel (AfDuS 158: 354 1929; see Wirz AfDuS 159: 311 1930) to such cases as suffer spontaneous amputation through the effect of encircling bands in association with palmar hyperkeratosis; see Ainhum (p. 1027).

PACHYONYCHIA CONGENITA

The condition is characterized by pachyonychia, acneiform and follicular keratoses, especially about the knees and elbows, symmetrical and circumscribed palmar and plantar hyperkeratoses, hyperhidrosis of the palms and soles, leukoplakia of the oral mucosae, and anomalies of the hair (Schäfer: AfDuS 148: 425 1924). The nails are thickened, opaque, lusterless and folded longitudinally, the changes being attributed to production of horny cells by the matrix, especially by that part of it distal to the part which normally contributes to the thickness of the nail plate. As a result this interesting malformation is manifested as wedge-shaped thickening of the nail plates, so that the distal edges may be several millimeters thick. The nails are narrow, laterally curved and distally elevated, with brown black, horny masses under the free margins.

Follicular keratoses somewhat like ichthyosis hystrix are found in the flexures; often they are thick, scaly and blackish or greenish in color. Volar keratoses in disseminated patches may occur, the patches frequently encircling the fingers so as to affect the dorsal as well as the volar surfaces, as in those

originally described by Jadassohn and Lewandowski (IkonogrDermatol, Urban and Schwarzenberg, 1906 p 29) as keratosis disseminata circumscripta tylomata et keratosis linguae. Volar hyperkeratosis accompanied by subungual hyperkeratosis was common among natives of the Upper Congo and in Uganda, according to Chalmers and Atiyah (JTropM 20 25 37 1917) whose description was entitled acanthokeratodermia praecornufaciens.

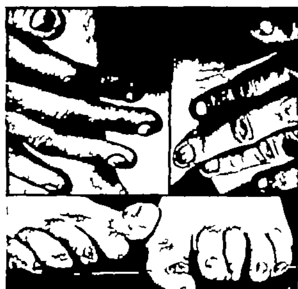




Fig 1344 —Pachyonychia congenita. (Dr D D. H. Cleveland.)
Fig 1345.—Acrokeratosis verruciformis, histologic structure. (Loveman and Graham ADS 43 971 1941.)



Fig. 1346 —Acrokeratosis verruciformis. (Drs A. B Loveman and P. J Graham.)

Cristy they stated, saw many similar cases in natives of the Upper Congo. While nail bed changes may alone be present fissured, nonerythematous thickenings of the epidermis of the volar areas were characteristic features. Arsenic might play an etiologic role in these cases though Chalmers thought not. Wilson (BJD 17 13 1905) described 3 cases of hereditary hyperkeratosis of the nail bed. Unna earlier described such an abnormality under the title

scleronychia. Association with alopecia congenita is common, as in the case of Sequeira (BJD 24 122 1912) A nonfamilial case was reported by Jordan and Rydnick (DZtschr 73 326 1936)

In an extensive review Kumer and Loos (WienKlinWchn 6: 174, 1935) classified pachyonychia accompanied by symmetric keratoses of the hands and feet occurring in association with (1) follicular keratoses of the body (2) keratoses of the body and oral leukoplakia (Riehl type, the commonest) and (3) follicular keratoses and corneal changes. Their patient, of the Riehl type was one of 23 affected members of 52 individuals in 5 generations in 1 family the abnormalities appearing as a dominant hereditary character

Relief was obtained in the cases of Garb (ADS 62 117 1950) by putting carefully fitted foam rubber insoles in the shoes. When the distal phalanges were amputated their patient was better off, reported Wright and Guequierre (ADS 55 819 1947) Mullins et al. (AD 71 265 1955) tried psychiatry

See Diasio (ADS 30 216, 1934) Hobbs (AmJMedSci 190 200, 1935) case; Tauber et al. (J 107: 29, 1936); Jordan and Rydnick (DZtschr 73 326, 1936) case with lesions present at birth; Touraine (PresseM 45 1569 1937) incomplete and aberrant forms Touraine and Granjon (BsocfrancD 44 649 1937) father and son; Hardwick (BJD 51 24, 1939) affected family Franks (UCutRev 46 439 1942) dominant inheritance Wright and Gross (ADS 47 436, 1943) association with leukokeratosis linguae, ? relation to avitaminosis A.

VERRUCIFORM AND PAPILLOMATOUS EPIDERMAL DYSPLASIAS

Epidermodysplasia Verruciformis of Lewandowski and Lutz (AfDuS 141 193 1922) is manifested by lesions present at birth, with no site of predilection for the first lesions, according to Wise (ADS 39 900 1939) The smallest are papules 2 mm. in diameter round oval or polygonal, with perpendicular margins smooth surfaces and pale red or reddish violet color without pigmentation. There are scales which are grayish in places, thick, yellowish greasy and removable in other areas. Lesions become disseminated fairly symmetrically over the whole body including palms and soles. Dorsa of hands and feet are usually affected. Plaques 1 to 2 cm. in diameter are the largest lesions, and transitional, confluent and lichenoid patches occur The scalp is involved from childhood on. The lesions respond to x ray treatment but soon recur Squamous carcinoma may eventually develop in some of them (Wise ADS 50 228 1944)

Degeneration and vacuolation of the epidermal cells are found to extend as deeply as the basal layer The similarity to verrucae planae is considerable though disarrangement of rete cells and pyknosis and fragmentation of nuclei may distinguish them, according to Sullivan and Ellis (ADS 40: 422, 1939) These authors listed 18 cases reported since the first 24 were collected by Mashkilleisson (DWchn 93: 560 1931)

Successful experimental inoculation of the disease from a woman to her sister who was also affected, was accomplished by Lutz (Dermatologica 92: 30, 1946) who reported a 15-year follow-up of these 3 patients who had ordinary warts on their fingers as well as the lesions of this curious disease. He offered the hypothesis that it represents a peculiar reaction to the wart virus.

The data on 75 cases were tabulated by Midana (Dermatologica 99: 1, 1949) He had no success with transplantation experiments. In 1 of his cases the oral mucosa was involved. He disagreed with Lutz's opinion that the disease represents generalized warts, but thought it a separate entity There occurred 14 cases in 4 generations of a family reported on by Niedelman (ADS 56: 45, 1947) and familial incidence was apparent in the case of Gustafson et al. (ADS 60: 912, 1949)

See Frühwald (DWchn 107 1401 1938), case Wendlberger (AfDuS 179 707 1939) case Costa and Junqueira (ADS 46 469 1942) squamous carcinoma developing on neck in 1 and 3 patients, brother and sister; Scolari et al. (YBD 1942, p. 221) review; Frühling and Bonjean (Dermatologica 91: 221, 1945) histology; Combes (ADS 53 421, 1946) case Caro and Pallin (ADS 60 872, 1949) case; Piers (Dermatologica 98 92, 1949) East Africa case Corson (ADS 61; 108, 1950) case.

Acrokeratosis Verruciformis (Hopf DZtschr 60 227 1931, AfDuS 167 344, 1933) resembles epidermodysplasia verruciformis, affecting dorsa of hands and feet. It is less extensive in distribution, and the basket weave vacuolation, parakeratosis and degenerative epithelial changes of the latter are absent. Loveman and Graham (ADS 43 971 1941) judged their cases, occurring in a girl and her mother to be nevoid. The histologic findings

distinguish Hopf's disease from that of Lewandowski and Lutz, for the lesions of the former are merely hyperkeratotic without parakeratosis or disturbance of the dermis (Ebert and Pearl ADS 57 462 1948)

Papillomatoses.—These rare and curious verruciform conditions were reviewed by Wise et al. (ADS 36 475 1937 39 596 900 1039 40 422 442 1939) Gougerot and Carteaud (AfDuS 160 232, 1942) described 3 forms of papillomatosis which are to be distinguished from epidermodysplasia verruciformis verruca plana juvenilis, and Darier's disease (1) punctate pigmented verrucous papillomatosis comprising 2 types, the punctate form of Gougerot and Clara and the verrucous form of Gougerot Clara and Bonnin; (2) confluent and reticular papillomatosis and (3) nummular and confluent papillomatosis.

PUNCTATE PAPILLOMATOSIS (GOUGEROT AND CLARA)—The 1 case began at 11 years of age on lateral portions of the body spreading over trunk and head within a year disappearing in the autumn and winter Punctate verrucous papules on the neck, trunk and extremities, scaling, stippled erythema of the scalp and face, and porokeratosis of the palms and soles comprised the three types of lesions found. On the face and scalp there were crusts, beneath which were small ulcers. The regions involved were the seborrheic ones. Treatment of all kinds failed.



Figs. 134 and 1348—Acrokeratosis verruciformis, a patient on whose neck squamous carcinoma developed. (Dr O. G. Costa)

VERRUCOUS PAPILLOMATOSIS (GOUGEROT CLARA AND BONNIN)—The 1 case began in adult life on the dorsa of the hands, wrists and forearms. Later the palms, neck and face were involved. The papules were elevated and rounded red to brown in color 1 or 2 mm. high, 3 to 5 mm. across. The scalp and volar surfaces were not involved. Itching did not occur Treatment was without benefit

NUMMULAR AND CONFLUENT PAPILLOMATOSIS.—The 1 case began at 13 years of age in the intermammary region spreading from there and most intense in the epigastric region. Small verrucous papules, pale red spots and pale red reticulum were the types of lesions present with confluence. No scales were present. Almost the entire trunk became involved, ... of the nummular lesions The scalp was unaffected, and the volar surfaces were not porokeratotic It hing was severe Histologic changes were in the elastica not the epidermis.

CONFLUENT AND RETICULATED PAPILLOMATOSIS.—The onset has been between the fifteenth and twenty fifth years beginning in the intermammary region and there most intense. Small, warty papules 1 to ... mm. in diameter were present dirty gray in color lacking scabness. The lesions tended to show median location on the trunk. Confluence occurred with the formation of reticulated patches isolated lesions being scattered about The scalp was unaffected The volar surfaces were not porokeratotic. Papillary ridges were found in the axillae. The eruption did not itch. The epidermis was slightly atrophic, and the elastic tissue was severely damaged. In the case of Wise and Sachs (ADS 36 473 1937) the absence of scaling was a difference from pityriasis versicolor The intermammary and epigastric regions were in-

volved particularly with confluence in the center. The mucosae were unaffected, and no systemic symptoms appeared. Histologic changes comprised mainly lamellated hyperkeratosis. Cases have been described by Hornberger (DWehn 121 361, 1950) whose patient, an old man was helped little by either arsenic or grenz ray therapy a d by Young (ADS 67: 594 1953), whose patient, a Negro woman, seemed benefited by thyroid.

Pseudo acanthosis nigricans is the designation given by Curth (AnnderD 78: 417 1951) applicable to a dermatosis occurring in obese, brunette individuals, affecting by predilection the folds of the axillae, neck, groin and mammary regions. Darkened, verrucose and rough patches or warty papules represent five of enhancement of the skin marki gs were noted in the folds, and a marbled or reticulated pattern occurred on the trunk. The lesions were filled by perspiration, maceration, pressure and friction and resembled those of acanthosis nigricans both clinically and histologically. The disorder showed a familial incidence. It tended in Curth's cases to disappear if the patient lost weight.

The similarities f pseudo-acanthosis nigricans and papillomatose confluente et réticulée are so striking according to Waisman (SouthMJ 46: 165, 1933) that they are probably identical. Compare case f Young a d Kesten (AD 7*: 182, 1935)





Fig. 1349 —Keratoma plant re sulcatum, in a nat of Dutch Guiana. (Aars ADS 24 270, 1931)

Fig. 1350 —Keratosis pilaris in a man.

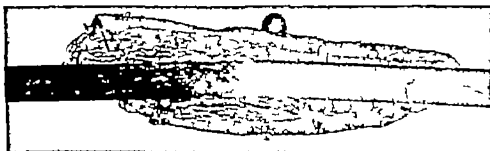


Fig 1351 —Hair with keratosis pila is plug ttached to it.

KERATOMA PLANTARE SULCATUM

This disease described by Castellani (JTropM 20 219 1917) and Mendelson (JTropM 27 39 1924) is a chronic affection of the soles seen in natives who seldom wear shoes and whose feet are constantly subjected to irritation. Aars (ADS 24 270 1931 JTropM 37 372 1934) reported a series of cases. He considered the cause as unknown The disorder as it affected aborigines of central Australia, especially the performers in corroboree dances, was stud

ied by Gray and Cleland (JTropM 35 125, 1933) It is characterized by marked plantar keratosis from which circular keratotic masses become detached, leaving characteristic punched-out holes. Cracks may extend through to the dermis often resulting in infection. Rest combined with the use of a keratolytic, such as salicylic acid constitutes the best method of treatment.

KERATOSIS PILARIS

Keratosis Pilaris is characterized by accumulations of horny material at the follicular orifices giving the affected surfaces a peculiar nutmeg grater like appearance Minute acuminate horny papules encircle the hair shafts at the mouths of the follicles. The sites of predilection are the quadriceps and triceps areas of thighs and arms. Sometimes the hair is coiled within the plug instead of piercing it. The condition occurs in skins which are naturally rough and dry and it is more pronounced in blonds and during the cold months of the year There may be some pruritus. Similar lesions are observed in avitaminosis A. A greaseless ointment base incorporating 1 per cent salicylic acid and large doses of vitamin A may be given and thyroid or estrogenic substances may help if the disorder is symptomatic of deficiency



Fig 1362.—Keratosis supra follicularis. H hair coiled up t the surface. M muscle. K, cut angulation f follicle, thought to be due to action of muscle. G coil gland. (Lane Histopathology of Diseases f the Skin, Macmillan, 1930, p. 291.)

Overdosage with vitamin A has been known to cause the condition (Sulzberger and Lazar J 146 788 1951 see Forman BJD 66 279 1954 review) Ordinarily keratosis pilaris represents a mild and trivial congenital and hereditary ectodermal defect, to be disregarded

Atypical Keratosis Pilaris, seen in the feeble-minded, was described by Coombs and Butterworth (*ADS 62 305 1950*) *as an* asymptomatic follicular hyperkeratosis with lesions scattered over the dorsum of the trunk, usually without involvement of the extensor aspects of the extremities. Pinpoint to pinhead size erythematous, follicular macules and punctate papules were seen, not occurring in groups. They varied seasonally and tended to appear in crops. Differentiation was given from seborrheic dermatitis and seborrheid. Therapeutic efforts were unavailing

Ingrowing Hair—In keratosis pilaris involving the bearded region, the skin should be kept soft and smooth by the use of a soothing cream, the beard

should be well lathered before shaving and a very keen razor once over employed. When ingrowing hairs develop they should be extracted as early as possible and tincture of iodine applied. (Greenbaum ADS 32 237 1935) See page 1318

KERATOSIS FOLLICULARIS CONTAGIOSA

Brooke (International Atlas of Rare Skin Diseases, 1892, 7: pl 22) of Manchester described an affection which resembled keratosis follicularis but appeared to be contagious. Most of the cases occurred in children. The eruption was symmetrical and more or less generalized. The sites of predilection were the nape of the neck, the shoulders and the extensor aspects of the limbs. The primary manifestations were those of a general corneous thickening with consequent deepening of the natural furrows of the skin. In these polygonal areas small, black, comedo-like points appeared and later developed into small spikes which projected outward a considerable distance. Later the horny plugs developed into large, brownish papules, the tips of which were still crowned with the straight or curved horny spicules. The papules sometimes coalesced, forming rough, yellowish-brown plaques. The skin was dry and harsh, never greasy and scaly as in keratosis follicularis.

The old descriptions suggest some underlying nutritional disturbance, such as avitaminosis A (see Elliot: JCutD 12: 162, 1894; Little: BJD 13: 417 1901) Hyperkeratosis affected not only the sebaceous and sweat orifices but also the intervening integument. Closure of the mouth of the follicle resulted in the formation of comedo-like cysts, or in deformities of the hair and of the whole follicle. The hyperkeratosis might be limited to the mouth of the follicle giving rise to lesions resembling those of keratosis pilaris, or it might involve the entire appendage, so as to form large, horny pearls which contained the remains of the hair follicle and also the contiguous sebaceous glands. The horny spines resulted from early hyperkeratosis of the follicular epithelium, a process which proceeded so rapidly that it forced the newly formed horny mass above the level of the skin, and the projecting spine really consisted of a series of inverted cuplike, corneous masses.

The disorder responded readily to treatment. Inunctions of an ointment containing iodide of mercury proved curative in Brooke's cases.

POROKERATOSIS

Synonyms.—Keratoderma eccentricum Hyperkeratosis eccentrica Hyperkeratosis figurata centrifuga atrophica

Symptoms.—The disorder was described simultaneously by Mibelli (GiorItalMalVen 28 313 1893) and Respighi (GiorItalMalVen 28 356 1893) The disease generally begins as a small slightly elevated wartlike papule which slowly enlarges peripherally and undergoes atrophy centrally so as ultimately to give rise to a circinate or crescentic plaque with a smooth, atrophic or callused center and a sharply defined, slightly elevated seamlike border Coalescence may produce polycyclic patches. The encircling dykelike border is grayish or brownish in color 1 0 mm. or more in height and commonly crowned with a linear horny ridge which is a characteristic feature and a slender furrow may run along its crest. Little milium like corneous bodies are embedded in the floor and in the sides and margins of the surrounding wall in some lesions. These masses, brownish or blackish in color and rounded or oval in shape are capable of being picked out.

The sites of predilection are the dorsal and palmar surfaces of the hands and fingers, the face and scalp and the sides and nape of the neck. The mucous membrane is occasionally attacked, the lesions here being white or opalescent and circinate or oval in outline Symptoms are slight. The development and spread of a lesion are tediously slow

Etiology.—The cause is unknown. Most patients have been males. No age is exempt Heredity may be concerned (Gilchrist: JCutD 15: 336 1897; Ducrey and Respighi: AnndeD 9 1, 1898) Wende (JCutD 17: 503 1898) succeeded in producing a lesion by transplantation. An excoriation was followed in a month by development of porokeratosis that in a boy with extensive involvement studied by Savage and Lederer (BJD 63: 187 1951) whose efforts to inoculate guinea pigs from their patient resulted only in foreign body reaction.

In consideration of the usual familial history the absence of histologic evidence of inflammation, the spontaneous disappearance of some cases, and the resistance of others to all but radical treatment, Lain (UCalRev 33: 283, 1928) interpreted the disease as a variety of the peculiar and specialized nevi. Hall (ADS 18: 296 1928) reporting 7 Chinese cases, also thought them nevoid and approved Mibelli original name kerato atrophic nevus.

Pathology.—The changes are mainly epidermal, comprising principally acanthosis with marked hyperkeratosis, particularly about the glandular orifices. Resulting pressure atrophy

Figs 1353 and 1354.—Porokeratosis. (Dr J Earle Moore)



Fig 1355.—Porokeratosis (Dr Charles E. Stewart.)



Fig. 1356.—Porokeratosis. (Dr Carroll S. Wright.)

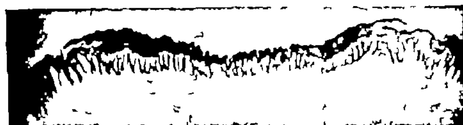


Fig. 1357.—Porokeratosis, sectioned so as to show topographically the peripheral walls and depressed center of the lesion. (Dr Carroll S. Wright.)



Fig. 1358.—Porokeratosis, showing region of junction of normal and abnormal epidermis. (Dr Carroll S. Wright.)

affects the rete, the papillary layer of the dermis, and the subjacent glands. Laminated corneum fills the mouths of the sweat ducts and ultimately occludes their lumina. Both hair follicles and glands are similarly affected by the gradual expansion of the plaque.

Prognosis.—The disease may start in infancy (Rosen ADS 45 782, 1942) and persist for life

Treatment.—The abnormality can be eliminated only by surgery

See Mibelli (MonatshPrakD 17 417 1893); Respighi (MonatshPrakD 18: 78, 1894) Hutchins (JCutD 14 373 1896) beginning on palm Joseph (AfDuS 39 335, 1897); Heidingsfeld (JCutD 23 39, 1905) case, review Matsumoto (JCutD 36: 276, 1918) histology, comprehensive review; MacCormac and Pellie (BJD 30 196 1918) extensive unilateral of upper extremity Sellei (DWchn 68: 241 1919), Wright (ADS 6 449 1921), case, review Hodara and Behdjet (DWchn 77 1168, 1923) histology Hitchi and Becker (ADS 26: 1021, 1932) finger Ambler and Stout (ADS 29 20 1934), Negro, Tamponi (AfDuS 175, 476, 1937), unilateral *upper extremity Miescher (AfDuS 181 532, 1940) porokeratosis annularis* Rosen (ADS 45 782, 1942), on neck since birth, Franks and Davis (ADS 48: 50 1943), unilateral wrist and hand involvement with dystrophy of nails, trophy of interossei and development of cutaneous horn Jones and Smith (ADS 56 425, 1947) review 2 cases Barber et al (NYSJM 48 1909 1948) pregnant patient, bibliography Hasselmann and Wernsdorfer (AfDuS 187: 331, 1948) unilateral zosteriform case Chakraborty and Das (CalcMJ 46: 112, 1949), familial Baski (ADS 60, 908, 1949), case spread slowly on leg and foot for 70 years Ayres (ADS 60 1218 1949) neck Ringrose and Nowlan (ADS 61 187, 1950), fissures Wilson (BJD 62 418 1950) angle of mouth and cheek Haber and Porter (BJD 63 23, 1951) unilateral, extensive.

CONGENITAL ECTODERMAL DEFECT

Anomalous formations of the ectoderm including its accessory structures are of occasional occurrence. They are frequently associated with other physical characteristics, so that the cases fall into distinctive groups (Kumer and Loos WienKlinWchn 48 174 1935) showing (1) symmetric volar keratosis with follicular keratosis of the body (2) keratoses of hands, feet and body with leukoplakia of the mouth or (3) these changes combined with corneal alteration or cataract.

Patients generally also present several of the following stigmas

Congenital dearth or absence of the sweat glands
Hypoplasia of the pilosebaceous apparatus
Alterations of nails, either hypoplasia or pachyonychia
Marked dental dysplasia
Thin, glossy smooth, dry skin
Intolerance of heat

The facial appearance is usually peculiar The prominent frontal bulge is due to exostosis of the inner table of the skull, as is also the depression of the base of the nose which is relative and not due to destruction of the nasal bones as in syphilis (Thannhauser J 106 908 1936) Fine wrinkles are seen about the eyelids and oral commissures. There is a hereditary tendency and while in many families this appears dominant and transmitted through mother to son in other families it is not sex linked and may affect females, according to Clouston (CanadMAJ 21 18 1929) who reported an analysis *of 119 cases* in 6 generations they were not of the anhidrotic type The hair and nail dystrophies occur in either sex and are transmitted by either sex, whereas the inheritance of the anhidrotic hypotrichotic-anodontia group is like that of hemophilia cases in the female being exceptional according to de Silva (QuartJMed 8 97 1939) in his review of 48 cases with bibliography

The anhidrotic group of patients whose difficulty in perspiration makes them intolerant of heat was segregated by Weech (AmJDisChild 37 766, 1929) who thought that diagnostically the cone-shaped incisor *is especially* significant. Milia are frequently present especially about the knees and elbows, in patients having normal nails and teeth but lacking hair (Smith ArchDisChild 4 215 1929 Sweitzer: ADS 27 1017 1933)

The earliest report of such cases was that of Thurmon (*ProcRoyM&Chir* Soc 31 71 1848) according to Lord and Wolfe (ADS 38 893 1938) who reported 2 patients in 1 family The classic triad in these cases consists of anhidrosis, hypotrichosis and anodontia or severe abnormality of the denture Fever and headache affected 3 brothers with this abnormality when they got hot and no eccrine glands were found in biopsies of their skins by Sunderman (AIntM 67 846 1941) Sweat glands are scarce but not absent in other cases which may be called hypohidrotic (Felsher ADS 49 410 1944) Fever was the presenting symptom in the case of Stiles and Weir (*J 158* 1432, 1955)

Etiology.—Little is known about the cause of these disturbances. Since some cases appear as mutants one is led to take note with interest of the fact that particular forms of mutation result in exceedingly similar abnormalities there is a family resemblance between unrelated patients. Irregular sex linked dominance appeared to explain the inheritance in an analysis of 19 families by Siemens (AfDuS 175 565 1937) Among the 58 cases reviewed by Koalund-Jorgensen and Christensen (ActaD-V 22 1 1941) only 7 were females.



Fig. 1339.—Hypotrichotic congenital ectodermal defect, sister and brother (Dr O G. Costa.)



Figs. 1340 and 1341.—Congenital alopecia syndrome with verrucose ichthyosiform dysplasia. (Dr Sam E. Sweitzer)

Treatment.—As in ichthyosis the patient must learn to live with his skin. If he cannot sweat he must avoid overexertion. Fissures and infections must be treated appropriately Plastic repair of nasal deformity was described by Lewin (AOtol 35 210 1942) Nasal symptoms were relieved somewhat by the administration of estrogenic substances by Clouston (CanadMAJ 40 1 1939) Orthodontic correction of dental deformities should be undertaken early in order to minimize facial abnormality (Upshaw and Montgomery: ADS 60 1170 1949)

CONGENITAL ECTODERMAL DEFECTS.—Compare Dyshormonal dermatitis, Osteodystrophia fibrosa, Pachyonychia, Simmonds' disease, Epidermolysis bullosa. See Mackee and Andrews (ADS 10 673, 1924) types of skin defects, review anhidrotic case; Mackay and Davidson (BJD 41 1 1929) hair and nail affected, sweat apparatus not, Rademaker (ActaPaediat 15, 37 1933) anodontia and hypotrichosis, Dods (MJAustral 1: 715, 1938) dental aplasia and skin changes Ellis and van Creveld (ADisChild 15 65, 1940) 2 children with ectodermal dysplasia, polydactyly chondrodysplasia and congenital heart disease Cole et al. (ADS 44 772, 1941) extensive linear atrophoderma with local pigmentation, telangiectasia, absence of skin glands Anderson (BMJ 2: 517 1948) Laurence-Moon Biedl syndrome, polydactylism, obesity hypogenitalism, retinitis pigmentosa, mental retardation, familial incidence Edit (J 138: 653, 1948) congenital defects associated with rubella, q v , Weber (MedPract 221 65, 1949) osseous and dermal dysplasias, review Jansen (Dermatologica 103: 167 1951), sixth case of anomalous pigmentation, atrophy of dorsum of hands and fingers, oral leukoplakia, oblit ration of lacrimal puncta, hemorrhag blebs on digits.

ANHIDROTIC ECTODERMAL DEFECT.—Gordon and Jamieson (AnnIntM 5 358, 1931) case review, Debré and Desbuquol (BullSocPéd 32: 235, 1934) case with volar hyperkeratosis Herbert and Garland (NEngJM 210 754 1934) case Schwarz (SouthMJ 28 606, 1935), 2 cases; Rinvik and Syrrist (ActaPaediat 23: 548, 1939) congenital anodontia and skin changes, Brenning (ActaMScand 105 88, 1940), case Friedman (UCutRev 44: 404 1940) case, with atopic dermatitis, Benedek (JID 4: 285, 1941), case with nail dystrophy; Brodie and Sarnat (AmJDisChild 64 1046 1942), anodontia; Ulmo (Dermatologica 90: 12, 1944), 4 cases in family Bruno nd Englehardt (AnnIntM 20: 148, 1944) 3 sibs; MacQuaide (Lancet 2 531 1944), 2 cases Osbourn (J 148, 844 1952) Negro with no teeth or breasts Wagner (ADS 65 543 1952) electrical skin resistance.

DYSKERATOSIS CONGENITA

Dyskeratosis congenita with pigmentation dystrophia unguis and leukokeratosis oris was the title under which Cole et al. (ADS 21 71 1930) described a remarkable young man who showed a peculiar scarflike pigmented eruption of the neck acrocyanosis of the hands and feet, hyperhidrosis of the palms and soles, dystrophy of the nails and a leukoplakia like eruption of the tongue and hard palate They found 2 similar cases and discussed the relationship of this concourse of abnormalities with dystrophic epidermolysis bullosa Darier s disease juvenile acanthosis nigricans and pachyonychia congenita which last seemed to them the most closely similar Two more cases of this kind were described by Garb and Rubin (ADS 50 191 1944) whose patients were partially relieved of oral symptoms, which included bullae at the labial commissures, by androgen therapy Evidences of adrenal abnormality in 1 of these patients was presented by Garb (ADS 55 242, 1947) Sisters afflicted with congenital cataract alopecia, hypoplasia of the nails and other abnormalities were reported by Cole et al (J 129 723 1945) and identified as examples of Rothmund s syndrome by Thannhauser (AnnIntM 23 559 1945) who suggested for this group of cases the designation *heredofamilial* atrophic dermatosis with telangiectasia. The 6 cases on record all males and including 2 pairs of brothers, were reviewed by Cole et al. (AD 71 451 1955)

Rothmund s Syndrome, Thannhauser pointed out, begins usually in childhood, and its occurrence in brothers and si ters of 1 generation is often observed. Werner's syndrome quite similar but manifesting itself in the second or third decade of life as a delayed manifestati n of multiple not merely ectodermal germ plasm defects, he would call hereditary familial atrophic dermatosis with skin ulcers. Both syndromes are recessive in heredity and in this respect as well as in other ways differ from the dominantly hereditary anhidrotic ectodermal defect (Thannhauser: J 130: 238 1946) Cataracts and poikiloderma with telangiectasis are the distinguishing features, and many cases have been reported under the misleading designation, scleroderma and cataracts, as by Mamon (These Paris No. 311, 1931) who collected 30 instances.

Cole (J 130 804 1946) was inclined to agree with the correction of the designation. He pointed out that incorrect classification had been committed also by Bloch and Stauffer (ADS 19 22, 1929) While the attempt had been generally made to classify these disorders under the two headings (congenital ectodermal dysplasia and Rothmund's syndrome) there have been so many *formes frustes* variants and so on that the physician has had to be very agile to keep ahead of the race. Cole et al. (ADS 61 529 1950) presented the girls they had reported in 1945 under the designation congenital cataract with congenital ectodermal dysplasia and noted that Rothmund (ArchfOphth 14: 159 1868) in his original description had placed his cases among those of ectodermal defect, despite the participation of mesodermal tissues in the abnormalities. The girls exhibited depressed saddle nose almost complete atrichia and an extensive eruption strikingly mottled, with dull red and pigmented changes surround g small wh te zones of skin. The cutaneous abnormalities were most noticeabl on the buttocks, ba k of the thighs a l legs, back cheek and arms Histologically the pilosebaceous apparatus was absent and the sudoral was diminished.

Cases have been described by Sch ler (SchweizMW hn 65: 719 1935) and Braley and Gartner (AOphth 1 492, 1930) Vitamin A was disappointing in the patient of Bruce (ADS 48: 560 1943) but it provided much improvement for the patient of Andersen (ADS 51: 94 1945) a woman whose glucose tolerance curve was diabetic.

Werner's Syndrome includes progeria like, thin, atrophic stretched skin which undergoes spontaneous ulceration on the exposed parts. The sclero-poikilodermatous abnormalities

do not appear until the second or third decade of life, and the skin changes are not those of true scleroderma. The early manifestations appear during the first and second decades of life with whitening of the hair, stunting of growth, and some atrophy of the acral skin, according to Reed et al. (BJD 65: 165 1953) Later the skin becomes atrophic appearing stretched over the underlying tissues and bony prominences. Especially on the spindly legs one may see fine, scaling variable pigmentation patchy atrophy and telangiectasis while tightness of the skin limits the motion of joints and leads to ulceration over pressure points. Circumscribed hyperkeratoses are a feature involving particularly the weight bearing areas, and the atrophic, telangiectatic skin under them is likely to ulcerate if they are removed. The nose is beaked bilateral juvenile cataracts develop, the hair is scant and fine the nails become dystrophic, and symptoms develop of hypogonadism, insulin resistant diabetes, osteoporosis, and metastatic calcinosis. Reed et al. demonstrated by electron microscope studies an obscuration of collagen fibrils with granular débris. Two brothers suffering from the disorder were presented by Sulzberger (ADS 36: 1256, 1937) Bilateral juvenile cataract, precocious graying of hair hypogenitalism, sterility, adiposity and typical facies are seen, and while the changes appear to represent pluriglandular dysfunction, they are not the same as those occurring in basophile adenoma of the pituitary lacking, among other features, the hypertrichosis of this condition. Aberration in hepatic metabolism of steroid compound seemed to be the primary disorder thought Bauer and Conn (TexasSMJ 49 852, 1953) Werner's syndrome with its defective metabolism of calcium, is nevertheless more closely related to pseudoxanthoma elasticum than to scleroderma, believed Smith et al (AD 71: 197 1955)

A table for differential diagnosis of Werner's syndrome Rothmund's syndrome myotonic dystrophy and progeria in children was given by Thannhauser (AnnIntM 23 559 1945) see Brodey and Ruppe (ADS 69: 243 1954)

Poikiloderma Congenitale was the designation given by Thomson (BJD 48: 221 1936) for a syndrome characterized by telangiectasia, pigmentation defective teeth and bony cysts. Hailey et al. (ADS 44 345 1941) described the fifth such case the first in America. Cursory examples of congenital atrophy with reticular pigmentation have been reported by Engman (ADS 13: 685 1926) Engman, Jr (J 105: 1252, 1935) and Gordon (BJD 52 255, 1940) These all appear to be related to dyskeratosis congenita, which may or may not, in individual examples, include cataract, and which may or may not become manifest early in life.

Thomson's syndrome as it affected 5 children and 1 man was described by Sexton (CanadMAJ 70: 662, 1954) All of these patients manifested all the features: development of lesions in early infancy on the traumatic areas of predilection (face and arms) with telangiectasia, pigmentation and fine atrophy, scant hair, loss of eyebrows, hyperkeratotic changes, and bone deformities. Bilateral cataracts developed at the age of 5 in three patients. The three others had yet to pass the age of decide ce for the onset. The additional features of a transient phase of sensitivity to sunlight with bulla formation, small stature, stubby fingers, and consanguinity only added to the complexity of the syndrome. A familial aspect was observed in three of the families involved. The author's adult patient had, in addition to the basic features of Thomson's disease hypothyroidism and elevated 17-ketosteroids with infantile testicle development and sterility. The almost complete absence of sweat gland and hair follicles with dystrophy of the large toe nails could conceivably place this patient in the group of congenital ectodermal dysplasias. Failure to utilize vitamin A suggested metabolic vitamin A deficiency.

Felty's Syndrome comprises chronic, deforming rheumatoid arthritis in association with splenomegaly lymphadenopathy leukopenia, cutaneous pigmentation and dusky nodules, and subfebrile temperature (Felty; BullJHH 35 16 1924; De Gruchy et al. PresseM 44: 377 1936) Slager and Levy (AIntM 57: 576, 1936) considered it the adult form of Still's disease a sepsis lenta perhaps due to *Streptococcus viridans*. A case of Still-Chauffard disease as seen by Hafsla (NorskMagfLaegevid 97: 173 1936) in a boy 14 years old, in whom it began at the age of 7 with arthritic symptoms involving the extremities and cervical spine; the cheeks were especially pigmented. Still (TransMedChirSoc 80 47 1896 1897) described a disease in children characterized by chronic arthritis, lymphadenopathy splenomegaly and leukocytosis, although some cases may show leukopenia. Schoch (ADS 66: 354 195_) doubted whether these syndromes are actually entities, but thought them representative of the coincidence of arthritis with hypersplenism. He called attention to the occurrence of ulcers of the legs in 5 cases of Felty's syndrome and observed lupus erythematosus cells in the bone marrow of 1 of them.

See Donner (DeutschMWchn 75 1251 1950), importance of focal infection; Kanar et al (WestJSurg 58 832, 1950) 2 cases treated by splenectomy with hematologic but not arthritic benefit Hutt et al (QuartJMed20; 57 1951), buccal ulceration associated with neutropenia relieved by splenectomy Rackow (BMJ 2: 1418, 1953) male 33 years old cured by splenectomy

Fanconi Syndrome.—Generalized brown pigmentation of the skin occurs in this rare disorder of children, which is manifested by the combination of severe, progressive, refractory macrocytic anemia, pancytopenia, hypoplastic bone marrow and various associated congenital defect such as microcephaly bony abnormalities, especially of the forearms and thumbs hypogenitalism and strabismus (Silver et al.; AmJDisChild 83: 14, 1952)

EPIDERMOLYSIS BULLOSA

Epidermolysis bullosa is a peculiar condition of the skin, usually hereditary characterized by the development of vesicles and bullae on even slight

traumatic provocation. It was first described by Goldscheider (MonatshPrakD 1 163 1882) see Riecke (HandbHuG 7, pt 2 222 1931) The disease is divisible clinically into 2 main groups the simple and the dystrophic, and the latter can be subdivided into 3 classes inherited in different ways (Hundley



Figs 1362 and 1363 —Epidermolysis bullosa hereditaria, with unusual bullae in concentric lesions. Scalp, eyebrows, lashes and hands involved. (Dr Grover W Wende)



Fig. 1364.—Epidermolysis bullosa, acquired, showing serous and hemorrhagic bullae, epidermic cysts, and cicatrices. (Dr Fred Wise.)

and Smith SouthMJ 34 364 1941) The cause is not known. Symptoms are usually worse in warm weather The severity ranges from relatively trivial involvement to such extreme fragility that the newborn soon dies (Black et al. J 129 734 1945 Lamb and Halpert: ADS 65: 369 1947;

Davidson: AmJDisChild 59 371, 1940) Even mild involvement is nevertheless likely to render one unfit for military service (Leider and Baer ADS 46 419 1942) A soldier for example who contracted scabies had a bad time with epidermolysis when he scratched (Samitz ADS 48 159 1943)

Cases in Negro children, representative of both the simple and dystrophic varieties, were reported by Joseph and Witherspoon (ADS 63 500 1951)

Mucosal involvement is rare but it may interfere with a baby's nursing (Corson ADS 49 382, 1944) Ocular lesions were reviewed by Cohen and Sulzberger (AOphth 13 374 1935) whose patient a boy 7 years old, suffered from bilateral corneal shrinking and scarring in addition to the standard cutaneous manifestations. Ocular involvement is rare.

The appearance of squamous cell carcinoma is occasionally seen the leg was the site in the case of Halpern (ADS 56 517 1947) and 4 cases were collated by Rasponi (abs BJD 62 514 1950) likewise affecting the leg in older patients they may have resulted from arsenical medication. A young man with scarring deformity from the disease developed a huge, curious, warty hyperkeratosis of the hand, which recurred despite plastic surgery (Melton AD 71 666 1955)

Four forms were differentiated by Bulow and Nørholm Pedersen (abs J 152 1575 1953)



Fig. 1365—Epidermolysis bullosa. (Dr T W Allworthy)

(1) Epidermolysis bullosa simplex, with dominant inheritance, in most cases persists through life but tends to improve. It was found in 96 of 256 members of 10 families, who lived mainly in 2 places in Denmark, Læsø and Vendsyssel. (2) Epidermolysis bullosa dystrophica differs morphologically from the simplex form and is often incapacitating and combined with other deformities. Inheritance is recessive, but milder dystrophic cases with mainly dominant inheritance are described. It was found in 31 of 200 members of 11 families. (3) Epidermolysis bullosa letalis was found in 9 cases of 67 members of 3 families there were also 2 infants who died from congenital malformations. (4) Epidermolysis bullosa, temporary form, is of brief duration and has a good prognosis. It was found in 4 of 89 known members of 2 families.

Epidermolysis Bullosa Simplex.—The subjects are well built and of average height and their hair teeth and nails are normal, as a rule. Bullae appear in early childhood and are located on areas exposed to injury and friction. The degree of trauma requisite to their production is variable In women they are more numerous just before the menstrual flow and less after the flow is established and also during pregnancy Most of the families are of German nationality but some are English, Irish or American, and one was Swiss and there is partial limitation to the male sex, the ratio being 59 to 41 (Cockayne Inherited Abnormalities of the Skin, Oxford U Press, 1933 p. 118) The presence of the condition is usually first noted in infancy although occasionally it does not develop or does not become apparent until later in life. The lesions consist of vesicles and bullae of various sizes which develop as a result of even slight pressure or irritation. They are usually filled with serum, but may contain blood. The susceptibility varies considerably in different persons. The lesions give rise to little or no pain or itching and generally leave no trace when they disappear but on parts of the body which are constantly exposed to trauma as the tips of the fingers, scarring and even

atrophy and loss of nails may result. A genealogic chart showing inheritance as a simple dominant character by 52 males and 65 females in 8 generations of a family of 283 members was presented by Noojin et al (ADS 65 477 1952)

Epidermolysis Bullosa Dystrophica, Dominant Form, is intermediate in severity between the simple and the recessive dystrophic forms, at least in the heterozygous state. Hallopeau (AnndeD 1896 p 453) established the variety which he designated as congenital bullous dermatitis with epidermic cysts. Epidermic cysts of the type described by him have frequently been noted as occurring in pemphigus and in other bullous disorders. Hale bodies and good teeth and hair are the rule but nails may be absent and are often greatly thickened and clawlike The lesions on healing generally leave thin, atrophic scars, associated with solitary or grouped milia

Epidermolysis Bullosa Dystrophica, Recessive Form, is characteristically observed in undersized simple-minded individuals whose nails are deformed and whose abnormal teeth are especially susceptible to decay (Tulipan ADS 37 22, 1938) The abnormality is present at birth or appears soon afterward and is universal in distribution The victims usually die young Slight trauma provokes lesions, which often involve the mucosal and conjunctival tissues (compare ocular pemphigus) Volar hyperhidrosis is a common accompaniment Epidermal cysts are typically present The relationship of these cases with congenital ectodermal defect (q v) is quite close The coincidence of epidermolysis and cutis hyperelastica (Danlos syndrome) was reported by Burrows (ProcRoySocM 25 1319 1932)

Guy's Type.—Three boys in one family were affected, all of whom appeared normal at birth. At the age of a few years, the hair of the scalp and eyebrows of each fell out and was replaced by fine hair only to fall out again. Bullae appeared particularly on the hands, feet, elbows and knees and healed without scar which is unusual. Cockayne placed this group in a separate class. See Guy (ADS 15 30 1927)

Wende's Type.—A boy was born with thick hair which fell out at the usual time but never grew back, leaving him completely bald. The skin lesions, early in onset, appeared especially about the orifices and spread gradually by the formation of new blebs about the periphery which healed to leave the skin firm, wrinkled, and scaly The skin of the hands, wrists, feet and ankles was affected and was sharply demarcated from the more normal skin of the forearms and legs. Cockayne placed this group in a separate class. See Wende (JCutD 20 53 1902)

Heinrichsbauer's Type.—The 2 abnormal children of this family had large area of necrotic and dark, bluish-red skin on all 4 extremities. Bullae were present at birth on the buttocks elbows and neck of both. Both died soon after birth. Cockayne separated this group from others. See Heinrichsbauer (ArchGynäk 134 673, 1928)

Macular Type.—A Dutch family has been studied by da Costa and van der Valk (ArchDuS 91 3 1908 DZtschr 60 195, 1931) and by Carol and Kooij (also ADS 37 97, 1937) wherein the infants by the age of 3 or 4 months developed a pemphigoid eruption the skin becoming spotty with diffuse brown pigmentation. Atrophic white spots developed first on the hands and feet and later on the face and buttocks. Dwarfism, microcephaly acrocyanosis and lack of hair were further features and the affliction appeared to be transmitted through the females to the males Most of those affected died young Cockayne (1933) segregated these patients as representative of a separate subtype and interpreted the inheritance as a sex linked recessive.

Atrophic and Albo Papuloid Bullous Dystrophy was described by Pasini (GiornItalD 69 336 1928) exemplified by cases such as those of Manganotti and of Polcaro (also YBD 1939 p. 230 '33) and of Whittle and Lyell (BJD 61 175 1949) See Ceratti (GiornItalD 74 335 1933) and Degos et al (BSocfrançD 1949 p. 104) Epidermolysis bullosa in these cases has its onset at an early age and produces not only bullae scars and pigmentation but also remarkable oval, circumscribed, but sometimes confluent white firm, elevated lesions wherein histologically one finds absence of the normal elastic tissue in the superficial dermis but a coarse feltwork of broken up elastic tissue below

Localized Epidermolysis Bullosa is recognized the feet alone or feet and hands being the only sites where noninflammatory bullae appear especially in warm weather following minimal trauma healing without scar sometimes associated with hyperhidrosis and manifesting inheritance as a dominant without accompanying dystrophies (Elliot JCutD 13 10 1895; Frank ADS 4 326 1943 Mosney ADS 50 167 1944 Johnson and Test ADS 53 610 1946) Warm weather blistering of the feet from infancy without dystrophic

changes or bullae elsewhere on the body occurred in 2 families and showed dominant inheritance according to the report of Anning (BJD 63 104 1951) Bullae on the hands were remarked by Lewis (BMJ 1 101 1948)

Cases were described by Cockayne (BJD 50: 358, 1938) wherein the feet suffered recurrent bullous eruptions and inheritance appeared to be a conditional dominant. The disorder appeared to be a separate entity rather than a variant of epidermolysis bullosa (Cockayne: BJD 59: 109 1947) It is also to be distinguished from tinea, pompholyx and impetigo, though these may complicate it secondarily Marked elevation of urinary porphyrins was found, and the elastic tissue seemed not abnormal in the case of Kierland and Harrison (PSMMC 15: 313, 1940)





Fig. 1366.—Epidermolysis bullosa, lingual bullae. (Dr Norman Tobias.)
Fig. 1367.—Epidermolysis bullosa, lesions of tongue and hands in a little girl. (Dr Robert M. Andrade.)



Fig. 1368.—Epidermolysis bullosa: elastic tissue stain, showing absence of elastic fibrils from papillary layer of the dermis. (Dr Stuart C. Way)

The disease received attention during World War II because military life proved intolerable to persons whose fragile skins tolerated less strenuous enterprise (Greenberg: ADS 49 333 1944; Franks et al.: UCutRev 49 57 1945; Walsman: J 1 4 1247 1944) An elastic bandage from ankle to knee seemed to reduce vulnerability of the feet reported Wiser and Orman (ADS 52 317 1943)

Etiology of Epidermolysis Bullosa.—The disorder is usually but not always strongly hereditary and its occurrence can occasionally be traced through several generations. In 3 patients who acquired but did not inherit bullous disease the cause appeared to be sulfonamide sensitivity reported Bloom (ADS 65: 625 1952 NYSJM 53 1077 1953)

Strands of fibrillar tissue normally extend from the dermis, terminate among the basal layers of the epidermis, and probably have a function in binding down the epithelium to the dermis. Such fibers are absent both from the lesions and from the uninjured skin of some cases of epidermolysis (Engman and Mook JCutD 24 55 1906 28 276 1910)

Sutton (J 54 1137 1910) confirmed this observation. Weiss (JCutD 35 26 1917) found similar alterations but Wise and Lautman (JCutD 33 441 1915) found the uninjured skin normal in an acquired case. Craig (AmJ DisChild 39 898 1930) was not able to detect the absence of the fibers in his case. The bullous lesions contain serum, leukocytes, and occasionally red blood cells. Separation of the epidermis takes place at the dermo-epidermal junction so that the fluid of the bullae does not contain epithelial cells (compare pemphigus)

Prognosis and Treatment.—The disease is incurable Extensive epidermal loss complicated by inevitable secondary infection may be difficult or impossible to control. Thus, severely afflicted infants die If an affected child survives his condition may improve considerably as the years go by No known effort succeeds in inducing the epidermis to adhere so that the extent to which it will adhere must be protected assiduously Atrophy and scarring are the sequelae of trauma which is carefully to be avoided (Tullpan ADS 37 22 1938) Pressure bandages such as are used in the treatment of burns, along with suitable antibiotics offer a good deal in palliation. The warm moist skin is much more vulnerable to bullous and bacterial complications than the cool, dry skin The patient of Schwartz and Levin (ADS 8 152 289 1923) improved following the administration of calcium lactate and parathyroid extract Beinhauer (ADS 32 469 1935) reported benefit with anterior pituitary hormone. A patient who acquired epidermal vulnerability at the age of 35 years was apparently cured by means of iron cacodylate a coagulant, calcium and small doses of x ray by Kittredge (ADS 30 537 1934) Pregnenolone 100 mg 4 times a day suggested by John Lamb helped a patient of Morgan (pers. comm 1954) Cortisone yielded good improvement in a girl with the hereditary dystrophic form of the disease reported Enell and Lindeas (Acta D-V 33 488 1953) Cortisone was of no avail in the newborn twins with the hereditary lethal form observed by Leland and Hirschl (AmJDisChild 87 321 1954)

See Bartle (ha J 112: 2002, 1939) 11 males, 14 females, f 55 members of a family affected with simplex form Waddell (JPediat 16 500 1940) 4 generations; Manner (J 120 1122, 1942) 30 of 72 ... Franks and Davis (ADS 47: 647 1943) 4 cases, 1 limited to feet ... Richard et al. (Revstomat 50 252, 1949) dental manifestations Thompson et al (... 42 647, 1949) dominant in 5 generations Cohen and Hopkin (ADS 62 220, 1950) ... case with progressive deformity of hands and ocular complications ... (J 145 1215, 1951) 13 cases in 4 generation in Jerusalem Feeny (BJD 65 379 1953) 11 cases of dystrophic type in 6 generations, lesions mainly on elbows and knees, Dowling and ... (BJD 66 139, 1954) 4 children in a family distinguishes dermatitis herpetiformis ... sebaceous ... of the soles does not occur

CONGENITAL SKIN DEFECTS OF THE NEWBORN

Circumscribed absence of the skin is in rare instances observed in the newborn. The defect is often solitary but lesions may be multiple and are then usually grouped or symmetric. The outline is sharply defined and circular or oval in most instances. The diameter is rarely more than 3 cm. The subcutaneous tissue is little affected and there is no evidence of inflammation. The site of predilection is the vertex of the scalp but the case of *Hahn* (quoted by Abt AmJDisChild 14 113 1917) presented integumentary loss over a large part of both sides of the trunk and Abt s patient had a defect involving the anterior aspects of both knees. Microscopically one finds absence of epidermal structures but no evidence of degeneration The cause is unknown, though amniotic adhesions have been blamed. Congenital skin defect may be a manifestation of epidermolysis bullosa (Carol and Prakken ActaD-V 21: 506 1940) but the lesions have not been related to trauma during parturition. They generally granulate and heal without, of course the development of epidermal accessory structures. The patient reported by Sutton (ADS 21:

855 1935) had scars on both sides of the trunk apparently the only instance on record in which the diagnosis was made in an adult. The cicatrices are to be distinguished from those of burns.

See Kahrer (MonatsbGeburtsh 31: 182, 1910) scalp case and 32 in literature; Walz (MonatsbGeburtsh 66 187 1924) 3 scalp cases, Streeter (ContribEmbryol 22: 1, 1930) relation to intrauterine amputation Terruhn (ArGynäk 140: 428, 1930) 16 cases in olving scalp, 33 others, relation to craniorachischisis and amniotic bands; Grieg (EdinMJ 38: 341, 1931); Ingalls (AmJPath 8: 525, 1932) dorsal midline anomalies in embryo Dowler (AmJDisChild 44: 1279 1932) Ingall (AmJObGyn 25: 861, 1933), scalp cases, review; Trillat and Cornut (Nourrisson 25 117 1937), forearm, Anderson and Novy (ADS 46 257 1942) 4 scalp cases, review; Rogatz and Davidson (AmJDisChild 65 916, 1943) defect of scalp, neck and extremities; Freud et al. (JPediat 27 591 1945) scalp involved in child and it mother Heisel (ADS 62: 917 1950) in triple scalp lesion, Weinhardt (DWchs 121: 312, 1950) aplasia cutis congenita circumscripta; Goldman (ADS 66: 590, 1952) thoracic and trunk.



Fig. 1369 —Congenital skin defect present at birth, long-healed, with symmetric scars of trunk (Button ADS 31 848, 1935.)

NEVUS

Nevus is a generic name for a malformation, usually localized and frequently congenital Nevoid means malformed in histogenesis. One notes that growth and development do not end with the event of birth. The name is loosely used, being applicable to pigmented moles, especially and also to hemangiomas, linear anomalies characterized by hyperkeratosis and verrucosity and other malformational abnormalities.

There may occur nevoid hyperplasia of almost any cutaneous structure. The changes may be confined to the sebaceous glands and periglandular structures, to the follicles or to the epidermal stratum Malformation may be primarily mesodermal rather than ectodermal Hamartoma Albrecht a term for overdevelopment or malposition of a tissue element in a site where the tissue normally occurs, comprises nevi with organoid structure Kyrle (Vorlesungen über Histobiologie der Menschlichen Haut, Springer 1: 207

1925) subdivided them into the "homologous," which resemble mature tissues, and "heterologous," which suggest origination from embryonic matrix. According to the character and preponderance of the cutaneous changes, various descriptive terms have been applied to the lesions. Thus *nevus spilus* means a pigmented macular nevus, *nevus pilosus* a hairy nevus, *nevus papillomatosus* and *nevus verrucosus* nevi which are covered with soft or hard, papillary excrescences, *nevus lipomatosus* fatty growths developing as nevi.

Failure of induction was the interpretation of Touraine (Minerva M 26 53 1951) in explaining from the viewpoint of Spemann's experimental embryology the whole range of nevoid disorders: early, late, mixed, systematized and regional. Nevi, seborrheic keratoses and neurofibromas were found associated with epilepsy by Yakovlev and Guthrie (ANeurol 26 1145 1931) who grouped the lot as "ectodermoses," a word like other "-oses," of appealing vagueness.

PIGMENTARY NEVUS

Pigmentary nevi are intumescences or superficial infiltrations composed of specific nevus cells. In color they range from pale fawn to bluish black and in size from a millimeter to many centimeters in diameter. In rare instances, as in the "bathing trunk cases," large areas may be involved (Lieberthal ADS 47 264 1943). Large ones structurally resemble small ones, although certain features may be exaggerated. The lesions may be solitary or many. In outline they are usually rounded or oval, but in shape, hairiness and distribution, they are subject to great variability. They are usually congenital but their development may be delayed even until puberty or later, as in the case of Arnold (ADS 40 386 1930). Measurements of the pain threshold indicated that nevi are more sensitive than normal skin, but neurofibromas are not (Davis and Pack ADS 70 268 1954).

Accessory mammary structures (polythelia) resembling pigmentary nevi are of frequent occurrence and should not be mistaken for them.

Extensive cutaneous nevi of both vascular and pigmentary types are sometimes associated with similar pathologic changes of the homolateral leptomeninges of the same dermatome (Netherton ADS 33 238 1936; Wilcox AmJDisChild 57 391 1939).

Nevi of the iris are frequently associated with ipsolateral nevi of the skin (Reese AOphth 48 271 1952).

Pigmented longitudinal stripes of the nail (q v) occur as a result of pigmented nevi of the nail root region.

Pigmented nevi frequently become larger and darker during pregnancy and this would seem to be no cause for alarm. Increase of pigmentation and the appearance of actually new junction nevi may occur in a patient who long receives ACTH (Goldman and Richfield J 147 941 1951).

Nevus Cells are usually large, pale and angular in outline with oval vesicular nuclei. They may be tightly packed, small and hyperchromatic, they may undergo atrophy and come to resemble fibrous tissue as in soft, fleshy moles. They may be massed or arranged in convoluted groups. Pigmentation, variable in quantity, is due to the presence of intracellular and free amorphous brown granules of melanin. Pigment bearing cells have been thought to be epidermal in origin, or dermal, or both, but this is controversial.

Masson (Annd Anatpath 3 417; 647 1926) supported the theory of Soldan (Arch Chir 59 261 1899) of the origin of nevus cells in nerve tissues and described the structure of the nevus as resembling Meissner corpuscles and neural tubes, the nevus cells in the upper dermis being arranged on these tubes like flowers on a stem. Silver staining methods were used by Foot (AmJPath 7 619 1931; 8 321 1932) in studying melanoma (q v) and benign moles corroborated Masson's interpretation of the nervous character of pigmented moles.

Nevus cells are dopa positive (Anatomy, pigment, p. 8). Ebert (ADS 37: 1, 1938) studied the clear cells of Merkel occurring in the basal layer of the epidermis and these he believed not to be tactile cells in fact but to be the parents of nevus cells when abnormal.

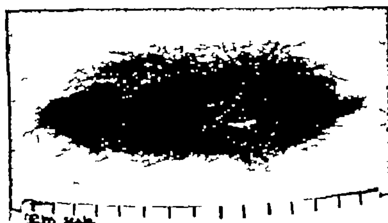


Fig. 1370.—Hairy pigmentary nevus.



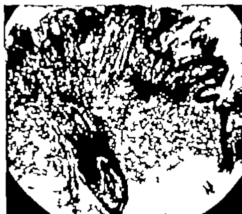




Fig. 1371.—Pigmentary hairy nevi "bathing trunk" lesion and disseminated moles (Dr F Ronchese.)

Fig. 1372.—Pigmentary nevus, benign cellular type (see Fig. 1373)

Fig. 1373.—Benign nevus cell tumor type "b" and "c" cellular

Proliferation of these cells would produce the histologic picture of intraepithelial formation of nests. Silver impregnation stains were examined by Jaeger (Dermatologica 93: 165, 1946), who found in intimate connection with nevus cells numerous neurofibrils from the myelinated trunks of the hypoderm. The pigmented mole was interpreted as a tactile tumor by Laidlaw and Murray (AmJPath 9: 827 1933) who found, in the tumors, nerve fibers which branched in a manner different from that which occurs in normal skin. See Becker (AmJCanc 22 17 1934); also Innes et al. (EdinMJ 46: 695 1939) The neurogenic origin of the cells is argued as acceptable in the interesting symposium of Moir Dawson et al. (BritJRadiol 19 217 1946)

Interpreting spatial proximity as indicative of derivation, Montgomery and Kernohan (JID 3: 465 1940) argued that dendritic cells are simply altered basal cells, that *cellules claires* are modified dendritic cells, and that multiplication of clear cells leads to the formation of nests of nevus cells in the epidermis: these authors claimed to have demonstrated the epidermal origin of nevus cells in the majority of cases studied. The cell nests appear to drop down into the dermis from their epidermal site of origin (Unna: Histopathology of the Skin Macmillan, 1896 p. 1137; Dawson EdinMJ 32: 509 1925)

Nevus Cell Tumors were classified histologically by Traub and Keil (ADS 41 214, 1940) as intraepidermal, intradermal, junction (those at the dermo-epidermal border) combination types, and blue nevi. The junction nevus they judged most hazardous. Becker (ADS 60 44, 1949) called lesions with nevus cells only in the epidermis type a, those with cells located only superficially in the dermis type b and those with cells deep in the dermis, associated with structures of Meissner s corpuscle and neural sort, type c. Combinations, such as a plus b b plus c and a plus b plus c, are common. When histologic indications of nevus cell invasion of the epidermis are present, the lesion is especially hazardous, Becker noted. The designation *junction* nevus ' is confusing and should be abandoned believed Becker (JID 22 21 1954) for this morphologic class, including as it does quiescent nevi, active nevi and lentigo maligna, is not definitive.

Limiting the term nevus ' to pigmented or nonpigmented lesions composed of melanoblasts, and the term melanoma to malignant cancer derived from these lesions, Allen (Cancer 2 28 1949) included among the nevi (1) junction nevi (dermo-epidermal or marginal type) (2) intradermal nevus (common mole or neuronevus) (3) blue nevus (4) compound junction and intradermal nevus and (5) juvenile melanoma. Since the junctional nevus seemed undoubtedly to him to be derived from epithelial cells, and since malignant melanomas arise from junction nevi, melanomas are therefore epidermogenic and should be placed in the category of *carcinomas*.

Cellular nevi have two origins, according to Masson (Cancer 4 9 1951): proliferation of intraepidermal melanoblasts and downward migration thereof; and proliferation of Schwannian cells of the dermal nerves and their migration upward. Fusion of these 2 primordia forms nevus tissue. During the time when melanoblasts migrate, the nevus is compound after migration ceases, the nevus is intradermal. The nevus cells of the dermis possess the characteristics of the Schwannian syncytium, so that one finds symplastic and retiform arrangement, isolation from the dermis by a collagenous sheath, and internal partitioning by a collagenous reticular membrane. Usually the nevic symplasm differentiates to form bundles and structures resembling Wagner Meissner corpuscles. Differentiation is progressive, reaching its maximum in the long-standing nevi of old people. The cells which drop off from the epidermis are melanoblasts, not epidermal epithelium. If it is true that they originate in the neural crest as do also the Schwannian cells in the dermis, the fusion of these two elements is comprehensible.

Nevi in children all show junctional proliferation, according to Stegmaier and Montgomery (JID 20: 51 1953) This is representative one may say of the embryogenesis of the nevus rather than of dangerous or malignant proliferation, and in fact mitotic cells are rare in juvenile melanotic lesions. Giant cells are commonly found in intradermal nevi and have no hazardous significance. There are more compound nevi in the age group of 5 to 19 years than at other ages, for it is during that period that the lesions undergo, for the most part, their development.

Correlation of clinical and histologic features was undert ken by Shaffer (AD 72 120 1955) whose morphologic categories comprised (1) flat lesions, macular pigmented spots; ( ) slightly elevated lesions, with slight palpable thickening; (3) halo lesions, elevated and su rou ded by pigmented macular areolae; (4) verrucoid lesions, showing fine digitate ex resce ces; (5) polypoid lesions, the surf ce bosselated (6) dome shaped lesions, moundl ke nd rising smoothly from the sirces; (7) sessile lesions, smooth surfaced, risi g sharpl from the tissue; and (8) pigmented papillomas, stalked or pedicled. Color and consi t ry were other variable features. Among the flat lesions, junctional features were pres t in 95% All of the slightly elevated nevi were compound or intra

dermal. All of the halo lesions showed some evidence of junctional activity. Of verrucous lesions, 77% showed junctional activity. All polypoid lesions were intradermal nevi. All sessile lesions were intradermal nevi. Of the dome-shaped nevi only 4% showed junctional activity. All papillomatous nevi were intradermal. It was apparent that considerable, but not absolute, clinical correlation with histologic structure exists and is of some value in its practical application.

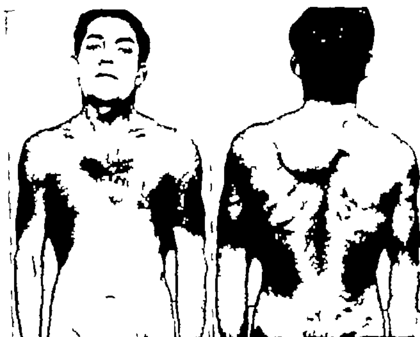


Fig. 1374.—Extensive hairy pigmentary nevus with cutis laxa of upper back. (Dr Robert M. Andrade.)



Fig. 1375.—Pigmentary nevus, benign cellular and neural ("mixed b & c") lesion. (Dr Frederick Weidman.)

Studies of the histogenesis and clinicopathologic correlation of nevi and melanomas were undertaken critically by Allen and Spitz (ADS 69: 150 1954) whose classification segregated the lesions as (1) benign: junctional, compound, intradermal, blue and juvenile; and (2) malignant: melanocarcinoma (superficial or deep) and malignant blue nevus (rare—they collected 6 cases). The forerunner of all malignant melanoma was, they believed, the junctional nevus or the junctional component of the compound nevus. Yet only a small fraction of junctional nevi become cancerous. Nevi on palms, soles and genitalia are almost always junctional or compound and should probably be removed prior to puberty. The hairy nevus

is usually intradermal and so benign, for the intradermal nevus is perhaps never the source of melanoma. Lack of elevation suggests the junctional form. The compound nevus appears to be a junctional nevus which has given rise to the intradermal component. Comprising as many as 98% of nevi in children, they constitute only about 12% of nevi in adults. Thus the common mole appears to be the evolutionary form of the originally junctional nevus. Juvenile malignant melanomas can be distinguished histologically from pigmented nevi, for they show superficially located giant cells, edema and telangiectasia, sharply delimited and compact clusters of epidermoid nevus cells, a characteristic form of spindling, and frequently associated abundant inflammation. The authors collected 5 cases, which differed from benign juvenile melanomas in lacking the morphologic characteristics and possessing distinctive anaplasia, so that they resembled deeply pigmented epidermoid carcinomas.

High fatality rate was associated, Allen and Spitz continued, with greater size depth, ulceration, pleomorphism of cells and numerous mitotic figures, but not with pigment content. In 337 cases, females showed significantly better survival rates than males. Mucosal lesions of head, genitalia and anorectal region showed the worst prognosis. Johnson (pers. comm., 1954) found that face and neck melanomas as compared with lower extremity lesions showed less malignancy and appeared at a later age in statistics from the Ellis Fischel State Cancer Hospital.

Multiple primary melanomas are not rare Allen and Spitz noted: some patients appear to manifest a diathesis for the development of junctional nevi and for the progression thereof into malignancy

In their review of the evidence concerning origin of nevus cells, they favored the hypothesis that direct transformation of epithelial cells into nevi occurs, and they questioned the evidence of neurogenesis.

When I have removed several nevi at the same time from 1 patient, it has been my experience that all of them show considerable similarity of histologic structure with respect to Becker s classification.

The junction nevus can be clearly distinguished by cutaneous microscopy of the living skin, according to Goldman (JID 16: 407 1951)

Prognosis.—Pigmentary nevi sometimes become malignant. *Increase in size increase in pigmentation* and *irritability*—these three symptoms singly or together are the early clinical evidences of change from benign to malignant melanoma (q v see Butterworth and Klauder J 102 739 1934) Extensive hairy pigmented nevi are the site of origin of melanoma rarely (Ebert and Oliver ADS 46 604, 1942 Conway Surg 6 585 1939 Woodburn et al. RockyMtMJ 51 281 1954) As a rule, persons with many nevi and neurofibromatosis are unlikely to develop malignancy a patient of Björneboe with v Recklinghausen s disease died, however with malignant melanoma. Apparently neurofibromatosis and benign or malignant melanoma are distinct entities, and a person with v Recklinghausen s disease is no more likely to have melanoma than is anyone else

Inflammation within a nevus, indolent follicular suppuration, is by no means rare (Duperrat AnndeD 81 251 1954) It is generally senile and is not painless.

Treatment—Dermatologists are unhesitating in removing brown moles for cosmetic reasons and are convinced they do not endanger their patients lives in so doing (Shaw SouthMJ 46 286 1953) The idea that all pigmented nevi should be excised is entirely impractical and would result in literally millions of unsightly and unnecessary scars.

When there exists doubt about the malignancy of the lesion, then the treatment for melanoma is appropriate destruction must be complete the full thickness of the skin must be sacrificed and the margin must be wide both laterally and in depth (Klauder PaMJ 33 472, 1930 Cannon NYSJM 40 1567 1940 Phillips (TexasSJM 42 645 1947; Traub: SouthMJ 40 1000, 1947) This destruction should be accomplished in one treatment not piecemeal. Excision is satisfactory The tissue must be examined *histologically* One removes any mole that bleeds or discharges; or is frequently irritated so that the patient s attention is attracted to it or is enlarging especially if it has arisen *de novo* in an adult, unless this is the normal enlargement accompanying pregnancy or is increasing in depth of pigmentation or is black or blue rather than innocently brown or is located on the palms, soles, genitalia, mucosa or nail bed (Chapman and Klopp MedAnnDC 23 308, 1954) The

large majority of facial ... ...ause they were inflamed
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...result in the removal of a ...e which is quiescent, one ... experience produce scars ...o use the actual cautery ...rn. The result is usually

Ronblad Strandberg Syndrome

— Skin finding of Pseudoxanthoma elasticum + Angioid Streak in Retina



...ediculate nevi, may have the ...les, 2 on the right and 1 on the ...pted] HALL 1 471 1930 com-

...s, especially on the front ...t be recognized early and ... w months. I do not like electro-sparking instruments for doing this work, judging them incapable of being handled with the nicety of the cautery Desiccating and coagulating instruments seal capillaries even at some distance from the point of their application and thereby make a resultant keloid likely

When asked to remove nevi for cosmetic reasons, one must advise the patient that pedunculated lesions turn out better than flat ones, and that a flat scar is the best possible outcome The scar f rthermore will be depigmented and will rem in so perhaps for years, a matter of concern when the patient is brunette and the lesion is located conspicuously Only experience ca teach one which nevi to treat and which to pass by and wh h patients will be appreciative and which, through fatuity and vanity will be hypercritical. When doubt exists, let the blemish alone.

T remove a nevus one secures local anesthesia and takes off the mass above the ...rea with a razor blade savi g such tissue fo histologic study The remainder is wiped

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with the red-hot point of the cautery so as to destroy what projects. The char is cleansed away with gauze moistened with alcohol. One develops the art of charring the right amount so that, after the wound heals, the scar will be neither elevated nor depressed. When the smooth burn is completed one applies Merthiolate, for example and allows the crust to remain exposed and dry or one may apply an occlusive dressing with tetracycline ointment. It takes about 3 weeks for the wound to heal.

The safety of removing nevi was attested by Ekblad (ADS 70 399 1954) among others he conditioned his approval upon routine histologic examination of tissue removed and adequate destruction of all that show junctional features.

Linear Nevus (Nevus Unius Lateris) is a nevoid growth which is arranged in fillets or streaks (compare ichthyosis hystrix) The neural systematization theory was proposed first by Bärensprung in 1863 according to Petersen (AfDuS 24 919 1892) The lesions may be unilateral or bilateral, involving one or several zones. The organoid tissue of which they may be composed may be representative of any cutaneous structure or accessory including defects which are verrucose papillary pigmentary syringomatous, sebaceous comedonic, hemangiomatous, lymphangiomatous, myomatous, myxomatous and neurofibromatous (Meirowski BJD 54 99 129 1942)

Ichthyosiform nevi involving mucous membranes are known (see p 1043)

If the nevus reaches the midline of the abdomen, its distribution there follows the linea alba. A linear nevus may be limited to distribution along the linea alba, as noted by Nicholas and Rousset (BSocfrançD 37: 830, 1930) Tobias (ADS 18: 451 1928) reported a case of extensive linear nevus, verrucose and pigmented, which involved the head neck, face and tongue and was strictly demarcated by the midline.

Broad bands of psoriasiform, hyperkeratotic and verrucous, scaly patches featured the case of MacKee (JCutD 37: 343, 1919) as in the case of Ormsby and Mitchell (ADS 1: 614 1920) Linear dyshidrosis with abnormality of the sweat ducts was reported by Ota and Ota (DWchr 103: 433, 1936) A mixture of tissues, sudoriparous, sebaceous and trichoepithaliomatous, affected the cheek and right side of the upper half of the body in the queer case of Milian et al. (BSocfrançD 39: 1220 1932)

Punctiform depressions within hyperkeratotic linear nevi are not rare; such a lesion affecting the hand was reported by Semon (ProcRoySocM 22: 349 1929) and I have seen one like it (compare keratosis punctata) while a comedo nevus of similar punctiform structure affected the pectoral region in the patient of Beatty (BJD 45: 346 1933) Naevus porokeratodes was the name given a similar lesion by Fabry (AfDuS 83: 113, 1907)

The blue nevus (q v) may occur as a systematized unilateral nevus especially when it appears as an extensive macular lesion, such as may be seen fairly often among the Japanese (Tanimoto abs ADS 43: 168, 1941)

A linear nevus appeared following x ray treatment of osteitis fibrosa cystica in a boy 13 years old (Bamber: BJD 47: 411 1935)

A zosteriform nevus was excised and recurred 5 years later reported Hallé (BSocPédiat 32: 297 1934)

Linear nevi which arch over the ear have, in my experience frequently been the origin of basal cell epithelioma, which recurs until the entire nevus has been destroyed a procedure better done at once than piecemeal. They are usually examples of nevus sebaceus (q v)

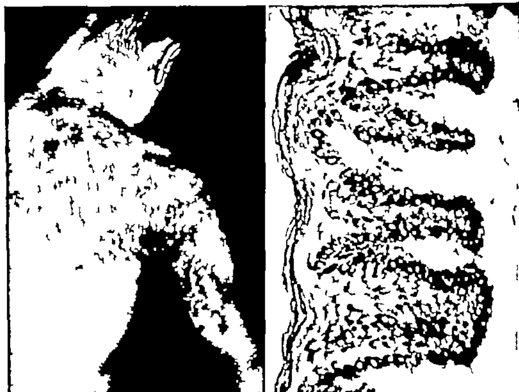
Many theories have been suggested to explain the peculiar arrangement in linear nevus. Montgomery (JCutD 19: 455 1901) reviewed these theories that the lines follow the course of the cutaneous nerves the lines run along Voigt's lines, the boundaries of peripheral nerve distribution the lines follow the lines of cleavage of the skin; the lines follow the course of the blood vessels the lines run in the metameres or segments of the body; the lines follow embryonic tissue expansions, the trends of growth of the tissues. The disorder is plainly one of organization, and research in experimental embryology may throw light upon the mechanisms involved (Huxley and DeBeer Experimental Embryology Cambridge U Press, 1934)

See Jadassohn (AfDuS 33 355, 1895) sebaceous; Dechet (ADS 40 829, 1939) resembling lichen planus; Park and Sunderland (AnSurg 43 341, 1941) the surgeon discovers the unilateral nevus; Arnold (ADS 51; 310, 1945), local patch of sebaceous and sudoral hypertrophy on the neck; Scholtz and Williamson (ADS 64 368, 1951) vitiliginous; Weber (BMJ 2 892, 1951) varieties.

Hypertrichosis and Melanosis.—Two examples appearing in the region of the shoulder following severe sunburn were seen in a distribution as of nevus unius lateris by Becker (ADS 60 155 1949) Hairy nevi, lacking pigmentation and nevus cells, comprising solely patches of hairiness, are occasionally observed (Squire BMJ 1 1265 1893) A curious area of melanosis without hairiness appeared at age 14 and persisted on the left shoulder region of a patient of Bettley (BJD 50 181 1938)

Mongolian Spots.—See p 789

Nevus Follicularis Keratosus (Comedo Nevus) —This systematized malformation, usually unilateral, is manifested as fillets of comedonic lesions. Dilated follicles are filled with epidermal detritus, and some of them are cystic. The crateriform or sievelike depressions dip into the skin along the direction taken by the lanugo hairs in the same region. The comedo-like lesions and



Figs 1380 and 1381 —Acquired, systematized, macular pigmentary and hairy anomaly (unilateral melanosis and hypertrichosis) Section shows epidermal melanosis with little indication of pigment activity Papillary and dermal chromatophores are evident, but no nevus cells are seen. (Becker ADS 60: 155, 1949)

cysts commonly undergo acneiform inflammation, with the formation of tender nodules which may resorb or discharge and heal with atrophic scarring Portions of the anomaly may require excision

Selhorst (BJD 8 419 1896) described a case of Naevus acneiformis unilateris, which involved the neck, thorax and upper arm of one side of a young man, in whom it had been present since birth. The case reported by Thibierge (AnndeD 7 1298, 1896) a girl, was similar White (JCutD 32 187 1914) described in a man 4 years old a bandlike lesion involving the right thorax from the lower angle of the scapula to the nipple, ranging from 3 to 5 cm. in width It had been present for 14 years, was asymptomatic, but spread slowly.

In a case of mine, remarkably extensive, a band in the axilla was so continuously inflamed that the linear mass of defective skin was excised. Grafting was not necessary although Wise and Satenstein (MedJ&Rec 137: 367 1933) recommended it, if surgical exigency demands. In my patient, the palm was pitted by a lesion which was obviously the extension of a band along the arm, forearm and wrist.

Histologically White found deep truncate tubular or irregularly shaped invaginations, dipping deeply into the corium and plugged with fat-

Distinction from pseudoxanthoma elasticum should be easy (Prakken: BJD 64: 87 1952) The case of Sachs (AfDuS 15_: 873, 1926) affected the back; that of Rothman and Henningsen (ADS 50: 59 1944) involved both extremities of one side of the body and the muscles were atrophic but no bony lesion was demonstrable; that of Appel (ADS 55: 716, 1947) was a linear sclerodermatoid lesion of an arm. Two curious cases were reported by Mears (BJD 63: 459 1951) and that f Webster and Hetreed (ADS 58: 482, 1949) resembled a keloid on the vertex of the scalp A crazy pavement nevus of the sacral region in association with Pringle's syndrome was reported by Walther (DWchr 124 940 1951)

Sclerodermoid Nevus is the title Ormsby (Diseases of the Skin Lea & Febiger 1937 p. 536) selected to describe an extremely unusual stiform, papular and pigmentary anomaly of the skin of the wrists, chest, shoulders and back of a young woman The papules were quite firm and had a moniliform arrangement. Fimerod found in it no consequential histologic lesions to account for the increased textural density I saw such a nevus systematized along the left upper extremity of a girl calcific nodules were present in some of the patches.

Nevus Lipomatosus Subepidermalis is a rare anomaly in which groups of tiny intracutaneous fatty tumors may simulate vesicles in the skin (Robinson and Ellis ADS 35: 486 1937). A well illustrated report of 6 cases was given by Nikolowski (DWchr 121: 785 1950) buttocks are the usual site. The typical hemispheric papules have a peculiar dirty translucent appearance, like oil stains on blotting paper Fat cells are most numerous in the papillary and reticular layer around the blood vessels and collagen fibers form about them a fine, fibrillary network which is metachromatic on staining with cresyl violet.

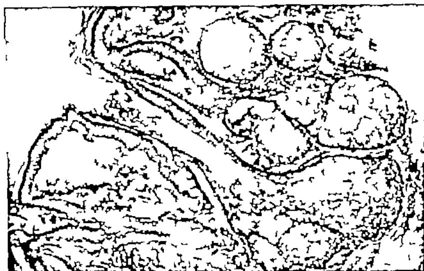


Fig. 1293 —Hypertrophic fat gland

Amelanotic Nevi.—These growths are similar to pigmentary nevi, but lack pigment. White moles may be large corrugated and cerebelliform. Rarely is one malignant but they may become so (see Melanoma amelanotic) Some nevi especially those of the neural type b or c have little or no melanin visible in them in gross specimen. Schwannoma is the title Becker (ADS 30 779 1934) applied to them, interpreting them as representative of proliferation of deeper nerve structures (see Neurilemmoma)

Cerebriform (cerebelliform) nevus is a large, corrugated lesion which may cover half the scalp and is composed of specific amelanotic nevus cells and neurofibromatous tissue (compare neurilemmoma) Plastic surgery is required.

See Klauder (J 90 1762, 1928) Wright (ADS 41, 1191, 1940) case Hammond and Ransom (Aberg 35 309 1937) 2 cases Cohen (BJD 57 173 1945) case; Klaber (BJD 57 16, 1945) case; Wise (ADS 60 988, 1949) large thigh lesion.

Leukoderma Acquisitum Centrifugum.—The lesion is vitiliginoid and round and in its center is a small, brownish maculopapule which is a circumscribed intradermal nest of cells resembling melanophores. The disorder is innocuous and requires no treatment. Sutton s disease is not very rare.





Fig. 1394.—Cerebriform nevus of occiput, a huge lesion later removed by excision and full-thickness graft. (Hammond and Hanson Arch Surg 35 309 1937)

Fig. 1395.—Cerebelliform mole.



Fig 1396 —Leukoderma acquisitum centrifugum, on left side of face and neck of a Mexican boy (Dr Robert N Andrade.)

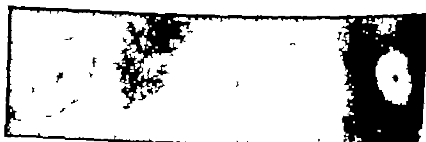


Fig. 1397—Leukoderma acquisitum centrifugum, on woman's back. (Sutton: J Cut D 34 797 1916.)



Fig. 1398.—Left: Blue nevus on dorsum of foot. Right: Blue nevus on dorsum of hand.

Fig. 1399.—Blue nevus of unusually large size on cheek. (Dr. Robert N. Andrade.)

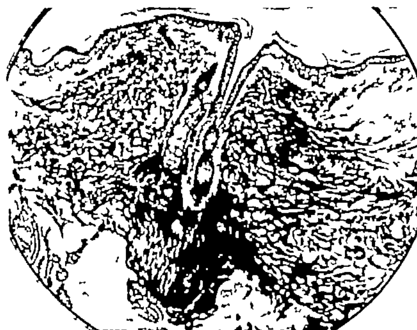


Fig. 1400.—Blue nevus, low magnification, H. & E. (Becker: ADS 21: 818, 1930.)

Sutton (JCutD 34: 797, 1916) reported 2 cases under this title. Shelmire (JCutD 35: 163 1917) added a third. Those described by Stokes (ADS 7: 611, 1923) and Peters (BsocfrançD 6: 34 1921) belong in the same category. A case was presented before the New York Dermatologic Society in 1884 (JCutVD 2: 189) and one was exhibited by Hyde in 1906 (JCutD 24: 84). Lomezynski (DWchn 82: 675 1926) carefully studied the condition and commented on its possible etiology. V Poor (abs UCutRev 29: 258 1933) concluded that the disease is one *sui generis*.

The central lesion is a nevus, according to Weber (BritJChildDis 21: 202, 1924) but the destruction thereof is not followed by repigmentation (Niles ADS 43: 357 1941). Of many lesions, some lacked the central nevus in the case of Netherton (ADS 19: 163 1929). The white area of a lesion in a patient with German measles remained white, and the application of a mustard plaster did not evoke erythema there (Feldman ADS 33 942, 1936).

Pigment cells may disperse or concentrate under a variety of influences, according to Leider and Fisher (ADS 60 1160 1949) who suggested that, when migration is peripheral vitiligo results, with its hyperpigmented areola and when it is central toward a pigmented nevus the result is Sutton's disease. Hebra was the first to note that vitiligo may commence close to a pre-existing pigment mole (Hebra and Kaposi Diseases of the Skin, Tay transl London, 3 180 1874). Depigmentation may begin about a lesion of psoriasis seborrheic keratosis fibroma papular sarcoid vascular nevus, or even lichen planus, according to Robinson (ADS 38 200 1938).



Fig. 1401 —Dermatosis papulosa nigra. (Dr Clyde L. Cummer)

See Busch (BJD 30 203, 1918); Goldhart (NederlTijdGeneesk 1, 1547 1920) "perinevral vitiligo"; Popoff (ZentralblHuG 22 474, 1927) mucosa involved; Montpellier (BsocfrançD [illegible] 31, 1922) following peripheral nerve injury; Mori (J pJDAU 35 623, 1934) 18 cases in literature, never on extremities; Richter (DWchn [illegible] [illegible], 1934); Gougerot and Carteaud (BsocfrançD 41 1536 1934); Feldman and Laskowsky (ADS 34 [illegible]0, 1936), "halo nevus"; Guequierre and Freeman (ADS 38: 242, 1938); Dracoulides (BsocfrançD 46 734, 1939) "nevus endo rtiligineux"; Kuske (Dermatologica [illegible] 232, 1941), lesions depicted in painting; Ayres (ADS 55 429 1947); Leider and Cohen (ADS 57: [illegible] 1948) review; Bocage and Perthuis (BsocfrançD 55 50 1948).

Acanthotic Nevus.—See Seborrheic keratosis (p 1176)

Anemic Nevus.—See p 1122

Atrophic Nevus resembles linear atrophic morphea (Andrews ADS 50 283 1944). Compare hemiatrophy hemangioma, and linear scleroderma.

Blue Nevus in its usual configuration is a blue-black, oval slightly elevated, firm lesion likely to be located on the dorsum of a hand or foot. The epidermis and upper cutis are normal, but in the dermis are circumscribed regions containing long irregular spindle cells filled with melanin. These tumors are benign almost invariably. Simple excision is curative but if one is sure of the diagnosis it does not need to be undertaken.

Montgomery and Kahler (AmJCanc 36: 527 1939) reported 65 instances occurring in 63 patients, suggesting that the lesions are more common than is generally thought. The onset in childhood of a firm, blue to blue-gray papule or nodule remaining as such without increase of size, generally permits clinical diagnosis. It is to be distinguished from melanoma (p. 1083), Mongolian spot (p. 789) and Hemosiderinotic histiocytoma (p. 1133).

The disorder was first segregated by Tièche (ArpathAnat 186: 212, 1906) in a report of 17 cases. See Farrell (ADS 26: 110, 1932); Miescher (HandbHuG Springer 12: 3: 1041, 1933); Marquardt (DWchn 104: 669 193)

Atypical forms received consideration by Kawamura (ADS 62: 893 1950) who classed them as (1) those combined with ordinary pigmented nevus cells under the epidermis in association with fusiform blue-nevus cells deeper; (2) those with a mere increase of pigment cells in the overlying epidermis; and (3) those combining blue nevus and fibromatous or myxomatous tissue changes. Kawamura s patient had a large, irregular macular lesion affecting the angle of the nose and adjacent cheek. A comparable, remarkable case was that of Upshaw et al. (Surg 22: 7; 61 1947), wherein the lesion was a linear nevus from 3 to 6 cm. wide and 17 cm. long on the left side of the chest. Extensive blue nevus, generally macular but sometimes showing nodules within its area, involving the side of the face and including the eye, was described as the nevus of Ota (naevus fuscocaeruleus ophthalmomaxillaris) by Dorsey and Montgomery (JID 22: 225, 1954) Examples have been reported by Parker and Beerman (ADS 59: 396 1949) and Cole et al. (ADS 61: 244 1950) The sclera and deeper structures are involved, including the ocular muscles, retrobulbar fat and even the periosteum f the orbit. Of the cases of Ot 's nevus reported by Dorsey and Montgomery 1 metastasized and caused death. They believed that transitional states between blue nevus, Mongolian spot and nevus of Ota occur

Dermatosis Papulosa Nigra.—Minute hyperpigmented, hemispherical papules develop in small numbers symmetrically on the malar regions or below the eyes as a common affection of Negroes. These benign lesions show microscopically irregular acanthosis excess of pigment in the basal layers of the epidermis and anomalous pilosebaceous structure (Castellani JTropM 28 1 1925 ADS 18 393 1928 Michael and Seale ADS 20 629 1939)

MELANOMA

Symptoms.—Malignant pigment bearing nevus-cell tumors usually but not invariably start in pigmentary nevi (p 1066) A small primary lesion may be overlooked and sometimes careful search reveals none at all. In the series of 317 cases of Affleck (AmJCanc 27 120 1936) 266 developed from pre-existing nevi, none of which was hairy While almost all nevi remain benign throughout life it is impossible to predict in a given instance whether this will be the case. Therefore, all such lesions are potentially dangerous. Those on the head feet and genitalia, and those which are especially liable to irritation are the most likely sources of trouble, according to Butterworth and Klauder (J 102 739 1934) In reporting 50 cases and analyzing 598 from the literature they found melanomas had developed from moles located as follows head, 16.5%; neck, 7 7% trunk, 15.6% genital and anal regions, 2.7% and foot, 52.3%

Multiple primary lesions, not excessively rare comprised 16 of 1,2○0 cases of Pack et al. (Canc 5 1110, 19○2) 12 of 337 cases of Allen and Spitz (Canc 6 1, 1953) The interval between the development of successive primary melanomas ranges from concurrence to several years.

Increase in size and increase in depth of pigmentation are definite danger signals, as are also increase in vascularity and an apparent chronic infection with slight tenderness (Brown and Byars: SGO 71: 409 1940) Junction nevi (q v) are especially dangerous. If a junction nevus makes its appearance in mature life it should be removed at once (Traub PaMJ 44 1103 1941) Traub (NYSJM 49 1661, 1949) thought all malignant melanomas originate from junction nevi.

A person who neglects irritation of a mole plays a part in his own self destruction (Cooke SouthMJ 21 117 1928)

A large proportion of the nevi which have become sore and have on that account been brought to me are cellular types b and c benign lesions with acne pustules in them.

Melanoma develops from pre-existing presumably once benign nevi in many instances, or it may commence *de novo* in the skin, eye or elsewhere. The origin is in pre-existing nevi in only about one fourth of the cases, according to the estimate of Becker (ADS 69 11 1954)

Melanoma ha been observed to be present at birth (Sweet and Connerty: AmJDisChild 62 1029 1941) Transplacental infection is recorded (Weber et al.: BMJ 1: 537 1930)

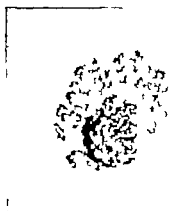




Fig. 1402 —Melanoma developing in a maligna t lentigo
Fig. 1403 —Malignant melanoma and regional metastases.



Fig 1404 —Malignant lentigo

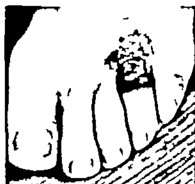




Fig 1405.—Malignant melanoma, toe (Drs. Butterworth and Klauder)
Fig. 1406.—M lanotic whitlow thumbnail bed.



Fig. 1407.—Malignant melanoma: cancerous nodule developing in melanotic nevus of buttock. (Drs. Butterworth and Klauder.)





Fig. 1408.—Melanoma: generalized cutaneous metastases. (Dr. J. W. Perkins.)
Fig. 1409.—Malignant melanoma of foot. (Dr. Otto Leslie Castle.)



Fig. 1410.—Malignant melanoma of heel. (Dr. Howard Morrow.)





Fig. 1411.—Melanoma of the eye.
Fig. 1412.—Melanoma of the eye. (Dr. Otto L. Castle.)





Fig. 1413.—M lanoma f nose.
Fig. 1414.—Melanoma of cl toris. (Dr. L. Halberstaedter.)



Fig. 1415.—M lanoma, gingi l primary in a Negro. (Courtesy of Dr. H. A. Baxter, Montreal, from Thoma, Oral Pathology, Mosby, 1934.)





Fig. 1416.—Malignant melanoma, widespread metastases. (Dr Perkins.)
Fig. 1417.—Malignant melanoma, widespread metastases. (Dr Schalek.)

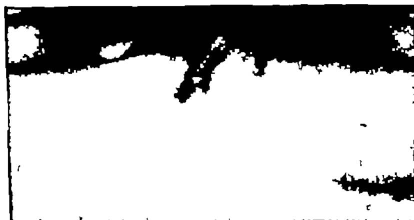


Fig. 1418.—Right inguinal metastases from melanoma of a man's back.



Fig. 1419.—Melanoma. The tiny primary lesion of the sole was mistaken for a hemangioma and treated by electrocoagulation. Patient died 3 months after photograph was made.

The case in which melanoma developed in the infant of a diseased mother reported by Gottron and Gertber (AfDuS 181: 91 1940) was attributed to infection by the mother's milk. Melanoma appeared in lymph nodes without a discernible primary in a patient whose arsenical dermatitis had healed with generalized spotty pigmentation (Rothman and Felsher: ADS 5.: 64, 1945) In a man I saw with melanoma in the axillary nodes, no primary source of any kind was detectable Numerous instances have been reported occurring in Negroes (Anderson: Surg 9 4.3 1941 Imler and Underwood SouthSurg 13 61, 1947)

When 3 cases appeared in 1 family Cawley (ADS 65 440 1952) reviewed the hereditary factors, which appear to be ordinarily of little concern.

An extraordinarily extensive case was reported by Way and Light (J 94 241, 1930) involving a woman 66 years old, practically the entirety of whose body was invaded, even the mucous membranes the onset so rapid as to resemble purpura hemorrhagica. There appeared pigmented stripes of the nail beds. The case described by Dixon (ADS 25: 574, 1932) was comparable.

A deeply seated, localized melanoma developed at the site of a tattoo caused by an indelible pencil (Sharlit: ADS 37: 301, 1938)

Melanosis oculi which may occur in association with ipsolateral skin lesions of the face as a systematized nevus, is frequently the site of initiation of melanoma of the eye (Doherty: AmJOphth 10: 1, 1927) See Reese (AOphth 29: 737 1943) The blue nevus (q v) in singular cases of the type described by Ota may be the origin of melanoma of the eye.





Fig 1420—Recurrence of melanoma. (Butterworth and Klauder: J 102 739, 1934)

Fig. 1421.—Pigmentation in malignant melanoma. The skin generally was diffusely bluish gray and the exposed parts were deep blue-black. (Odel et al.: PSMMC 12: 742, 1937)

The coloring matter is melanin, not blood pigment as in Kaposi's tumor Pigment is present in the secondary growths, and may be present in the urine General pigmentation may occur especially of the exposed parts (Odel et al. PSMMC 12 742, 1937 Trueblood NoWMed 46: 199, 1947; Fitzpatrick et al JID 22 163 1954 Møller abs J 157 1059 1955) In a patient who excreted pigment in the urine thiouracil brought the color back to normal while it was being given (White JLabClinM 32: 1254 1947)

Ulceration and bleeding are late symptoms. They mean that action has been delayed until it is probably too late The primary tumor enlarges, becomes nodular papillomatous, perhaps fungating and sloughing and intracutaneous satellites appear about it. The disseminated cutaneous lesions are pinhead to egg size ovoid, moderately firm in consistency and brownish or blackish in color

The course of the disease generally is rapid but is quite variable. Metastasis usually first reaches regional lymph nodes and is there limited for a time, but it may first become general via the blood stream. The liver and lungs are commonly invaded in a massive manner and the heart brain and other organs become widely infected. Melanoma has been known to metastasize to other tumors, such as a myoma of the uterus or a fibroadenoma of the breast (Edit J 139 1161, 1949)

The patient generally maintains a fair state of well being until the terminal stage then declines rapidly Perhaps as many as one-fifth of patients dying of metastatic melanoma die of a cerebral lesion, the symptoms simulating an apoplectic stroke but without the usual improvement that follows a mere hemorrhage. The brain shows at autopsy a large, blood filled cyst lined with melanoma.

Spontaneous regression of melanoma that has already metastasized was observed in a man reported by Levison (BMJ 1 458 1955) who found a few comparable cases in the literature including 2 described by Bennett (Lancet 1 3 1899) In these singular instances, regression of metastases followed removal of the primary tumors.

Malignant Lentigo —Lentigines (q v) are in fact junction nevi macular and small, but certainly capable of serving as the origin of melanoma. It is possible that a high proportion of melanomas which arise from no lesion previously recognized by the patient do arise from one of these seemingly innocent and inconspicuous abnormalities.

Hutchinson (DMedWchn 30 1378 1904) originally described malignant lentigo (see Dubreuilh AnndeD 5 1092, 1894 Bayet also AnndeD 6 495 1895) The lesion is macular dark gray-blue or brownish black, sharply marginated with an outline made up of irregular arcs. It may not appear homogeneous but rather to be made up of confluent elements.

It should be excised widely full thickness.

See Dubreuilh (AnndeD 1912, pp. 129; 205; also JCutD 31 834, 1913); Kob (DeitrKlinChir 137: 703, 1922) Cord (BJD 51 84, 1939); Klauder and Beerman (AD 71 2, 1955)

Melanotic Whitlow —Under this title, Hutchinson (BMJ 1 491, 1886) described a malignant disease of the nail bed characterized by the evolution of melanoma in the perionychium.

Hertzler (ADS 6: 701, 1922) reported 2 cases and gave an important review of the disease. Womack (ArchSurg 15: 667 1927) added 4 cases. The patient of Dickson and Jarman (AnnSurg 95 470 1932) was a Negro. Newell (SouthMJ 31: 641 1938) added 1 case to a collection of 38 and found reports of 9 examples antedating the original description of Hutchinson. See Mason (Surg 5 47 1939) Duperrat and Cintract (AnndeD 7 235 1947)

In many cases, injury has apparently played some part in causation. The majority of the patients are middle-aged or elderly individuals.

The disease is diagnostically to be distinguished from paronychia felon granuloma pyogenicum subungal hematoma, chancre and gangrene. Pigmentation may not be marked, but it can always be found at the edge of the lesion perhaps forming a threadlike elevated band.

Treatment is prompt amputation at the metacarpophalangeal joint or its pedal analogue unless more must be sacrificed.

Amelanotic Melanomas are recognized (Farrell ADS 26 110 1932) They differ only in lacking the pigment which is more or less profuse in ordinary melanoma. Diagnosis depends on histologic examination. Metastases from an amelanotic lesion developed pigment when they grew beneath the epidermis in the man seen by Dotha and Lennox (JPathBact 67 90 1954)

See Symeonidis (Klechrpath 47 33, 1934) case, bibliography; Stout (AmJCanc 33 196, 1938) thigh lesion resembling Paget disease; Nordentoft (ActaRadiol 26 115, 1946), arising in birthmark on forehead, autopsy; Stout (JMoMA 46: 248, 1949) auditory canal lesion; Kindler (BJD 62 174, 1950) bizarre psoriasiform lesion of forearm; Hecht (ADS 671 369 1953) spindle-cell lesion on nose with metastases.

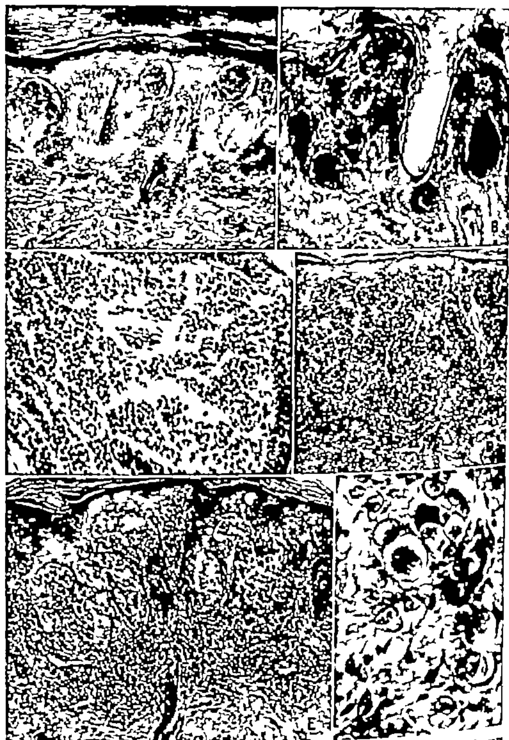


Fig. 1422.—*A*, Quiescent smooth brown nevus (Type AB) from sole of woman 33 years old, no clinical change for years, no sign of activity or malignancy. *B*, Active black nevus which appeared 4 months previously on cheek of girl 8 years old; nevus cell groups and epidermis intensely pigmented, and melanophages in dermis. (*A* and *B* from Becker: JID 22: 217, 1954.) *C*, Elevated pigmented nevus, dermis filled with strands, cords and masses of nevus cells (Becker: AmJCanc 22: 17, 1934). *D*, Early melanoma in a nevus. *E*, Lentigo maligna, diagnosed by pronounced round cell infiltrate and groups of malignant cells being cast off at the surface (*D* and *E* from Becker: MinnM 34: 1161, 1951). *F*, Lymphatic metastasis from lentigo maligna, showing pronounced anaplasia. (Humphreys and Becker: Pigment Cell Growth, Academic Press, Inc., New York, 1953, p. 109.)

Pathology Diagnosis and Prognosis of Melanoma.—In view of doubt regarding histogenesis of the lesions, the name melanoma has met with approval (Dawson EdinMJ 32: 509 1925) See nevus cells (p 1066) and pigment formation (p. 787) Melanoma is the neoplastic proliferation of nevus cells. Melanoma cells are dendritic in vitro and their processes are full of granules. They do not resemble ectodermal cells (Grand et al. AmJCanc 24 36, 1935, 33 394, 1938) melanoma in tissue culture produces alkali which inhibits its growth, while neutralization of the alkali encourages growth.

Pathologic changes indicative of malignancy are hard to describe inva sion of the epidermis is suggestive of malignancy of a pigmentary nevus (q v) the junction type of which is the most hazardous. Melanin may be shed in parakeratotic keratinization over a melanotic lesion in either a benign or a malignant mole (see Merenlender AfDuS 162 322, 1930 Dargeon et al. Cancer 3 299 1950) Becker told me that melanin granules, which tend to be of the same size within one cell in benign or malignant lesions, are more varied in size and quantity in malignant moles than in benign ones. Dependence is to be placed on the history of progress in the lesion (Greenblatt et al.: SouthMJ 29 1936) and when the microscopist is in doubt the clinician should be radical.

Histologic criteria of malignancy (discussed also in connection with pigmented nevus, q v) as observed by Couperus and Rucker (ADS 70 199 1954) were (1) inflammatory infiltrate at the periphery of the lesion, (2) more than an occasional mitotic figure (3) giant cells with single bizarre nuclei, (4) marked pleomorphism, (5) general enlargement of all tumor cells, and (6) tumor cells and mitoses in the epidermis. Provided that 3 or more of these changes are present and associated with junctional features, the di agnosis of primary malignant melanoma may be made with assurance.

One must differentiate seborrheic keratosis hemosiderinotic histiocytoma, blue nevus, pigmented basal cell tumors, and small purplish angiomas. Microscopic examination provides the final criterion see Montgomery (MedClin NoAm 28 968 1944) Illustrations supporting the hypothesis of ectodermal genesis and distinguishing nevus cell tumors from seborrheic keratoses (acanthotic nevi) were published by Dawson (BritJRadiol 19: 219 1946)

Biopsy was judged to be a safe procedure to be undertaken if indicated, wrote Ackerman (JKansMS 50: 60-A, Aug., 1949; AmJClinPath 18: 602, 1948) in reporting on 75 cases, 26 of which originated on the lower extremities and 24 on the head or neck. The diagnosis is especially difficult, he thought, if there be little pigment present, although the dopa test might be helpful. Even if microscopically the lesion appears malignant, a lesion in a child of prepuberty age is almost never a source of fatal disease.

Histologic malignancy in the 3 infants among 63 cases of DeWeese (J 138: 1026, 1948) was not associated with metastasis. Rarely does a child die of melanoma, reported Spitz (AmJPath 24: 591, 1948); the abrupt rise in malignancy after puberty suggests a hormonal influence in the acceleration f growth. The few known cases of malignancy in young individuals were reviewed by Coffey and Berkeley (J 147: 846 1951) whose patient, a 7 year-old girl had a sacral lesion and inguinal metastases. Despite the presence of metastases in the 4 children they discussed, resection of the metast tic lesions appeared t be well worth undertaking See Truax and Page (AnnSurg 137 255 1953)

Metastatic melanoma in the skin does not provoke the histologic picture of the junction nevus, and the absence of such change reliably distinguishes primary from secondary cu taneous melanoma (Allen: Cancer : 28, 1949)

In a review of 934 cases, Allen and Spitz (Cancer 6: 1, 1953) observed a dispropor tionately greater incidence of primary lesions of the soles, female genital mucosae and head and neck regions. They diagnosed multiple primary lesions in 12 instances. They felt it strongly advisable to search seemingly cured patients from time to time, seeking new junction nevi which, if found, should certainly be removed. They found 4 instances f malignant blue nevi, which are quite rare. In cutaneous melanoma, according to their figures, the out look is better in women than in men. Melanomas arising from mucous membranes they found to be almost invariably fatal.

Malignant melanomas can be distinguished from benign pigme tary nevi by Geiger counts of the lesions after i travenous injection of P^{32} in a dose of 100 to 150 μc, for the counts how significant differences not observed in cases of benign lesions or basal cell or squamous carcinomas, according to Bauer and Steffen (J 159: 563, 1955)

Treatment.—Melanoma which seems not to have disseminated should be excised radically (Taussig and Tonney: CalifWM 52: 15 1940; Driver and

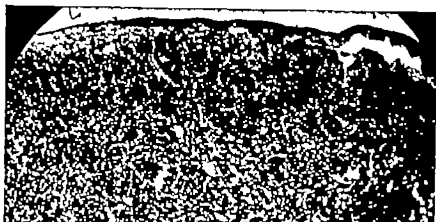


Fig. 1423.—Malignant melanoma, composed of melanin-laden spindle cells.



Fig. 1424.—Malignant melanoma, showing nests of malignant cells, intraepidermal on the left, intradermal and accompanied by inflammation on the right. (Dr Stuart Way.)

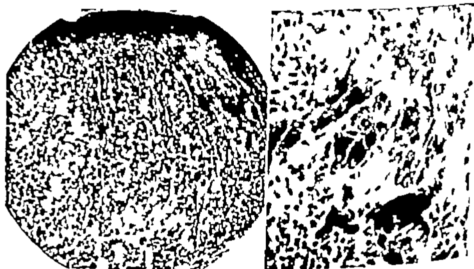


Fig. 1425.—Melanocarcinoma. (Dr Fred Weidman.)

Fig. 1426.—Melanoma, a case initiated by indelible pencil injury. (Sharlit: [illegible] 37: 301, 1938.)

en masse excision of the primary lesion with its entire lymphatic drainage basin and the dissection of the regional nodes in continuity See Gordon et al. (The Biology of Melanoma, NYAcadSc, 1948)

There appeared to be little difference in survival rates among patients treated by lymph node dissection routinely and those whose nodes were resected only if there were clinical indication of involvement, in the series of 90 patients of Clarke (AustralNZealJSurg 22 8, 1952) One may believe with Sulzberger and Baer (YBD 195-, p. 235) that adequate local excision does about as well as the mutilating procedures which have lately been recommended by a number of cancer surgeons.

Survival for 5 years without recurrence is not secure proof of cure (Fanger and Roberts NEngJM 246 813 1952) Secondary lesions have been known to turn up actually decades after the removal of a melanoma, and every experienced pathologist knows that each case of this disease is likely to be in some way remarkable The interval between the removal of the primary and the appearance of pulmonary lesions was 11 years in a patient of Galgano (J 152 518 1953) and after that the patient survived for 9 years longer

Hope need not be abandoned even in the face of local recurrence or regional metastasis. Distant metastases are sometimes solitary and, if symptomatic, may be removable with palliation. In a patient of mine such a tumor caused intestinal obstruction, and its resection was followed by prolonged good health. Some cases with regional node metastases have been cured (Daland and Holmes NEngJM 220 651 1939) and the increased probability of cure by adequate surgical work should not be denied any patient. Melanoma is not to be attacked by x ray for the lesions are only exceptionally radiosensitive (Ellis BritJRadiol 12 327 1939) although some authors would give caustic doses of radiation therapy after surgery (Williams and Martin Lancet 1 135 1937), and others have used radiation therapy alone (*Anderson* and Simpson AmJRoentg 33 54 1935 Reitman AmJRoentg 67 256 1952)

See Gilchrist (JCutAGUDis 7 117 1899) nevi and melanocarcinoma, 2 cases, 1 in Negro Johnston (JCutD 23 49, 1905) excellent study several types of cases; Broders and MacCarty (SGO 23 28, 1916) 76 cases; Coley and Hoguet (AnnSurg 64 206, 1916) 61 cases use of Coley's serum; Stark (JCancRes 3 279 1918) hereditary pigment-producing tumor in Drosophila, Hazen (SouthMJ 13 245, 1920) 7 cases, valuable review Gleave (Lancet 2 658, 1929) 40 cases, Ewing (BMJ 2 852, 1930); Amadon (JMichSMS 29 713, 1930), 77 cases Marino (J 103; 202, 1934) anorectal primary Lile and Schonberg (AmJMedSci 191 340 1936), cure after lymphatic metastasis Passey (JPathBact 47 349, 1938) in melanoma in Japanese 1 dogs; Nogata (abs ADS 37 112, 1938) only 5 cases of metastatic melanoma with neck nodes cured (?) literature, Smuts (SoAf MJ 13, 287 1939) nasal septum primary with neck nodes Sikh (AmJCanc 36 Verse (DWchn 165 620 1939) small primaries and large metastases Sikh (AmJCanc 36 243, 1939) urethral primary cases; Schörch (DeutZtschrChi 252; 277, 1939) hemopyrrole rabbit melanoma Pack and Adai (Surg 5 47, 1939), 477 cases; Smith (ArchOphth 22 437, 1939) nasal mucosal primary Fishback (AmJCanc 40; 471, 1940) melanoma after removal of extensive congenital pigmentary nevus Moersch et al (J 115 2142, 1940) 21 cases central nervous system Moragues (AmHeartJ 19 579 1940), cardiac metastases in about half of cases, rarely suspected clinically Peller (CancRes 1; 538, 1941) review Chotosky (AnnSurg 113 392, 1941), 117 cases, 5-year survival rate 42%; Stough (TexasSJM 37, 676, 1942), primary lid margin and conjunctival cases, Taylor and Tuttle (ArchPath 38 66, 1944) primary of uterine cervix Mason et al. (PSExperBiol 66 421, 1947) chemistry of melanin from mouse melanoma, Mulligan (CancRes 9 615, 1949) cancerous and noncancerous melanomas in dogs Ewing (JIndianaMA 42 317 1949) 65 cases melanuria not necessarily fatal; McCune (AnnSurg 130 318, 1949) of 40 Walter Reed cases, 7 of 12 clinically negative lymphatics were histologically positive Wright (JPathBact 61 507 1949) 222 cases of skin, mucosae and eye, Mohs (ADS 62 269 1950) escharotic treatment Pissetti et al. (abs J 146 1951) mucosal melanomas Escovitz and White (AnnWestMSS 4 338, 1950), rectal primary with calcification in metastases Lowsley (SouthMJ 44; 487 1951), prostatic; Hall et al (SGO 95 184 1952) 159 cases Russi et al. (SouthMJ 46; 336, 1953) primary meningeal cases occur in diffuse and nodular forms, review Hisel et al (J 153 712, 1953), cardiac metastases in 12 of 34 melanoma autopsies Norris (NoWMed 52 622, 1953) only 16% survival in 1,000 cases followed 5 years although no metastasis present when originally treated Madden (ADS 69 106, 1954) curious example of lymph channel spread; Becker (ADS 69 11, 1954), in pregnancy; diagnosis and treatment, Byrd and McGanity (SouthMJ 47 196, 1954) bad prognosis, Alexander (Laryng 64 133 1954), 93 nasal cavity cases, 25 originating in septum, Riddell and McIlwain nosis, Tompkins (Cancer 6 1215, 1953) ulceration of bad omen (AmSurg 20 827, 1954) 63 Vanderbilt University Hospital cases, 70% clinically nonpigmented McWhorter and Woolner (J 156 695, 1954) juvenile melanoma and melanoma in children Mason et al. (CancRes 14 648 1954) melanin granules incite strong agglutinins in rabbits, however tagged antimelanin gamma globulin does not localize in melanomas specifically

NEUROFIBROMATOSIS

Robert Smith of Dublin published in 1849 a complete study of 2 cases with necropsy and dissections of each (Fulton NEngJM 200 1315, 1929). Smith denied the nerve origin of the fibrocellular tumors, a point of view in

which he has not been alone, though the weight of evidence is with v Recklinghausen (Ueber die multiplen Fibrome der Haut, Berlin, 1882) who interpreted the tumors as nervous.

Symptoms—The lesions of Smith Recklinghausen disease develop in and beneath the skin as sessile, pedunculated or flattened, painless tumors. They may be present at birth but usually appear at or after the age of puberty The onset is said in many cases to have followed unusual exposure to cold (Zipperson: DZtschr 70 279 1935) Multiple skin tumors are often associated with nerve tumors. Anomalous pigmentation, particularly in the form of coffee spots, and imbecility and epilepsy are occasional accompaniments. Osseous and endocrine changes are sometimes noted. Heredity is involved in only about 15% of the cases. Occasionally the growths may be single, pendulous and large. As a rule they are multiple numbering from 3 or 4 to 100 or more. In size they range from that of a small pea to that of a turkey egg They are usually velvety smooth, rounded or oval, with a narrow and somewhat elongated neck, but they may be pear or sausage-shaped, or even lobulated, and sessile or even subcutaneous. In their early stage, and in some instances throughout their course elevation is slight or *wanting and the tumors are more apparent to touch than to vision. The integument covering the tumors* is pinkish in color lax and soft. The trunk is a favored site for the lesions, but the face and limbs are frequently affected. The mouth, the rectum in fact the entire intestinal tract, and even the bones may be involved.

A great variety of *formes frustes* are seen, including those in which macular pigmentation is the only manifestation (Wise and Eller J 86 66 1926)

The lesions may be unilaterally limited in distribution to the region supplied by a nerve especially by branches of the trigeminal.

Cases fall into 4 groups (Weber BJD 21 49 1909)

(1) Plexiform neuroma, without multiple molluscoid tumors and with or without pigmentation (including elephantiasis nervorum, macroglossia, and local o ergrowth); (2) multiple molluscoid tumors without obvious nerve trunk tumors, and with or without pigmentation; (3) pigmentation without (or as yet without) obvious nerve tru k or cutaneous neurofibroma; and (4) anomalous cases, complicated with lesions of the bones o epidermic changes, this group incl ding the famous elephant man (Levin and Behrman: ADS 41: 490 1940)

Gastrointestinal Involvement—Megacolon in a horse was shown by Pick (BeitrPathAnat 71 560 1922) to be due to neurofibromatosis of the splanchnic nerves which supplied that portion of the gut (see Neurinoma) A large neurofibroma of the stomach was reported by Shouldice (CanadMAJ 15 66 1925)

Pigmentation—In some generalized cases freckling and pigmentation are concomitants that are fairly characteristic but not pathognomonic. Pigmentation may precede or accompany tumor formation.

Pregnancy—There usually occurs growth of the tumors during pregnancy along with increase of pigmentation and the development of pain or tenderness in the nodules (Sharpe and Young J 106: 682, 1936; AIntM 59 299 1937)

Molluscum fibrosum gravidarum is the peculiar variety of fibroma in which the lesions develop during the later months of pregnancy, and partially or completely disappear post partum (Brickner AmJObGyn 53 191 1906; AmJDermat 16 240 1912) The tumors are pinhead to pea-sized, pedunculated and almost exclusively confined to mammary cervical and clavicular regions. Hirst (AmJObGyn 63: 2_6 1911) described a case, and Sutton (AmJMedSci 147: 419 1914) reported 2 instances of the disease, both in young white women of more than average intelligence. Histologically the lesions cannot be differentiated from those of Recklinghausen s disease. See Ward (BJD 2_ 153 1913); Sharpe and Young (J 106 682, 1936) The lesions are benign and easy to remove by means of dermatologic instruments for minor surgery



Fig 1428.—Smith-Recklinghausen disease, showing myriads of nonpigmented, velvety protuberances, and their appearance at close range. (Photographs by Emil Forney)

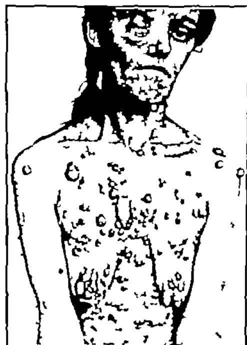




Fig. 1429.—Molluscum fibrosum. (Drs. L. H. Anderson and Frederic Tice)
Fig. 1430.—Cutis pendula, a form of neurofibromatosis



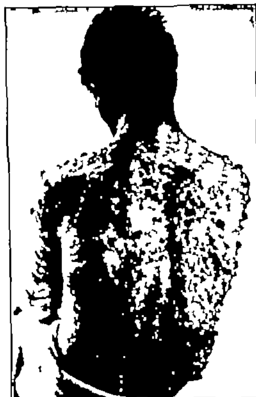


Fig. 1431.—Neurofibromatosis. (Drs. John A. Murray and Arthur S. Brumbaugh.)
Fig. 1432.—Molluscum fibrosum. (Dr John [illegible].)





Figs. 1433 and 1434.—Neurofibromatosis, with cutis laxa of eyelids. (Dr Robert N Andrade.)

Fig. 1433.—Neurofibromatosis, showing café-au-lait lesion of right pectoral skin.



Fig. 1434.—Neurofibroma.

OSSEOUS INVOLVEMENT.—Bone cysts associated with pigmentation of the skin were described by Brooks and Lehman (SGO 38 587 1924) and Lehman (ADS 14 178 1926) Abnormalities include scoliosis, dysgenesis of individual bones, pedunculated subperiosteal tumors and irregularities of bone shape and cysts, especially in the bones of the skull, as in the case of Heine (MünchMWehn 74 239 1927) Unsuspected osseous lesions may be disclosed by x ray examination of patients with cutaneous neurofibromatosis. The influence of innervation on the growth of bones was discussed by Penfield and Young (ANeurPsych 23 320 1930) whose patient a young woman, had lesions of the skin, spinal cord, brain and acoustic nerve Tumors of the Nervus Acousticus was the title of the monograph in which Cushing (Saunders 1917) described 13 such cases, stressing the relationship with Recklinghausen s disease. The syndrome of bone cysts, chloasma and premature puberty described by Robson and Todd (Lancet 1 377 1939) fits here compare Osteodystrophia fibrosa.



Fig. 1417.—Molluscum fibrosum gra idarum.

OTHER FEATURES.—Adenoma sebaceum (Pringle EdinMJ 40 260 1900) is said to be a frequent concomitant. While some authors attempt to unite within one syndrome v Recklinghausen s disease and the combination of tuberose sclerosis with Pringle s disease (p 1151) they can be distinguished clinically and histologically and their coexistence has not been demonstrated, according to Carol and v Heusden (AfDuS 175 1 1937) whose study of 31 cases and review of previous records indicated that the cases may be divided into types characteristically pigmentary osseous, elephantiasic and tumorous, of local or of general distribution. The development of subungual lesions was followed by Fröhlich (DWehn 109: 1211 1939) Rille (DWehn 101 1432, 1935) described a characteristic facial expression dreamy apathetic, resigned, melancholy but not morose. The interrelationships between epilepsy neurofibroma and nevi, grouping them all under the designation ectodermoses, were considered by Yakovlev and Guthrie (ANeurol 26: 1145 1931) They called attention to the common systematization, apparently neural, with involvement of one or a group of cutaneous nerves, particularly the trigeminal.

COMPLICATIONS in the cases of Carol and v Heusden included deafness, 16%, pain, 13% hemorrhage 10% psychosis, 3% and malignancy 1% Surgical complications were discussed by Jones and Hart (AnnSurg 110: 916,

1939) including the possibility of hemorrhage into a pachydermatocele. Optic atrophy in association with neurofibromatosis was reviewed by Dresner and Montgomery (QuartJMed 18 93 1949) who reported 3 cases.

MALIGNANT COMPLICATION —It is rare for malignancy to supervene; when it does, it is generally in the form of locally recurrent spindle-cell sarcoma (compare dermatofibrosarcoma see Speed AnnSurg 116: 81 1942) Deep neurofibromas are dangerous (Carache: AmJSurg 41: 275 1938) These lumps are movable, noninfiltrative tumors, scapular axillary gluteal abdominal, and of the extremities. Radical surgery is the best treatment.

No nerve fibers could be found in the sarcoma which proved fatal to a young man with neurofibromatosis studied by Potter and McWhorter (AnnSurg 90: 397 1929) In 61 cases studied by Preston et al. (ArchSurg 64: 813 1952) there were café-au-lait spots in over 60% osseous changes, mental disorders and diseases of the eye affected some 20%; and sarcoma developed in 10 of the patients, 8 originating in deep tissues, 1 in the cutis. Of the sarcomas, 3 were cured by surgery and 4 were not operable Metastases were proved in 5 instances, of which 4 involved the lung Of 6 patients subjected to surgery for sarcoma, recurrences took place in 3. The sarcomas were fibrous, spindle-cell and neurogenic. They were not radiosensitive.

Etiology—The cause of neurofibromatosis is unknown. Its association with endocrine disturbances is probably as cause rather than effect. Many authors have noted a familial tendency Adie (ProcRoySocM 19 11 1926) gave especial consideration to the inheritance of the disease and familial incidence was reviewed by Castellino (UCutRev 34 384 1930) whose 2 patients were brother and sister The defect is a simple dominant, according to Cockayne (Inherited Abnormalities of the Skin Oxford U Press, 1933) without any sex limitation in most families in a few families it is inherited as a dominant but there may be an inhibiting gene or dominance is incomplete There is insufficient evidence to show whether in the isolated and familial case it is inherited as a recessive or not but in them there is a definite limitation to the male sex. The frequent association of the disorder with developmental defects of various kinds is suggestive The relationship with xanthoma (q v) and with tumor acousticus (Gerundo and Corwin JKansMS 39 250 1938) has received attention, but nothing is actually known.

Pathology—The histogenesis is still debatable. V Recklinghausen held that the lesions are neurofibromas, and that they spring primarily from the connective tissue sheaths of the nerves, afterward spreading upward along the nerves. Nerve fibers run through them usually widely separated from each other The perineural histogenesis theory of Verocay was approved by Gray (ANeurol 22 91 1929) who studied 2 cases terminated by sarcoma. The specific histology was described by McNairy and Montgomery (ADS 51 384 1945) Melanotic nevi occurring coincidentally are probably essentially distinct See Pigmentary nevus Neuroma Neurilemmoma.

Treatment—If the malformation is limited to a small region, such as one side of the face the lesions may be excised or otherwise destroyed with a view to cosmetic improvement. In widespread cases nothing can be done and the lesions are best let alone for fear of their recurrence. When individual lesions cause trouble by exerting pressure, by occluding or obstructing or by undergoing necrosis ulceration or hemorrhage they must of course be attacked surgically They are not at all responsive to x ray therapy Improvement followed the administration of sulfathiazole, 2 Gm per day given for another purpose (Weiss J 128 909 1945) Hemphill (1947) showed me a woman whose lesions diminished notably after injection with thiodinamine (Fibrolysin Merck) unfortunately this patient was lost to follow up

See Thomson (On Neuroma and Neuro-Fibromatosis, Edin., Turnbull and Spears, 1900); Weiss (ADS 3 144, 1921), Negro case; Wayson (ADS 37 421 1938), Hawaiian cases; Schröder (BeitrKlinChir 164 561, 1936) heredity in 1176; Touraine and Roland (... 43: 603 1936) achromic nevus, 3 cases; Newmann (DWchn 107: 1481, 1936) orbital tumors causing blindness Kahn (APediat 56, 150 1939) multiple abnormalities in infant Mason et al. (AmJDisChild 57 331, 1939) affected child developed malignant thoracic neurofibroma; Tas (ActaD-V 21 699 1940) myelin stain technic Lavender and Prentice (ArchSurg 40 ... 1940) silent intrathoracic lesions; Uhlmann and Grossman (AnnIntM ... 225, 1940), bone changes; Loftis (ADS 42 657 1940) identical twins; Chalkley and Bruce (AmJDisChild 64 ..., 1942) umbilical lesion associated with extensive involvement of intestine and

mesentery; Touraine and Ruel (AnndeD 6: 1, 1946) hereditary polyfibromatosis; Barker (ADS 56: 782, 1946) mother and daughter; D'Abreu (BritJTuberc 41: 8, 1947) thoracic neurofibroma; Lindenmeyer (SchweizMWchr 77: 398, 1947) intestinal form Lichtenstein (ANeurol 62 822, 1949) pathology Parker (BMJ 1 1177 1950) involvement of vegetative nervous system; Meredith (SouthMJ 44: 1142, 1951) involvement of cauda equina; Love and Dodge (SGO 94 161, 1952) 60 cases of dumbbell neurofibromas affecting spinal cord, Kocsea et al. (AmHeartJ 44 981 1952) association with pheochromocytoma Scott and Wooding (AmJDisChild 84 446, 1952) cases in Negroes.

Elephantiasis Nervorum is the name applied when neurofibromatosis affects a limited region in a diffuse manner so that the part is grossly enlarged or deformed Among the numerous and picturesque synonyms are pachydermatocele (Mott) elephantiasis mollis (Virchow) plexiform neuroma (Verneuil) elephantiasis molluscum (Nélaton) neuroma cirsoideum (Bruns) and fibroneuroma racemosum (Rizzoli)

A remarkable series of cases in which the scalp was affected was collected by Helmholz and Cushing (AmJMedSci 132 355, 1906) The commonest location is the scalp and the lesion is likely to begin as a brown spot which in early years begins to sag In the surgical removal of one such lesion, Helmholz and Cushing had great difficulty in controlling bleeding Their dissection of the tissue removed revealed neurofibromatous involvement of the innervating auriculotemporal branch of the trigeminal nerve.



Fig. 1438.—Local overgrowth in Nairobi native boy (Dr A. L. Rebeiro.)

Compare Cutis verticis gyrata. An extremity is a possible location for such a pachydermatocele The involvement is likely to be unilateral. Dermatolysis and cutis hyperelastica are probably Recklinghausen's disease with widespread peripheral distribution. They too are sometimes unilateral. The broad, lax, pendulous tumors which sometimes occur in Recklinghausen's disease appear to consist mainly of fat and thickened skin and generally involve the face arms, axillae buttocks or thighs. Eichenlaub (ADS 3: 152, 1921) reported a case which clinically resembled a linear nevus; the tumor involved the forearm and consisted of a pendulous, lobulated, doughy mass, present since birth (Fig 1378) The case of Graham (JCutVD : 105, 1894) was quite similar as was that also of Schneiderman (ADS 1 : 483, 1925) Sutton, Sr saw one in private practice All involved the forearm and hand. These cases are examples of peculiarly localized elephantiasis nervorum. Spittel and Fernando (BMJ 1 696 1929) described involvement of an entire leg, the tissue of which examined after amputation was composed of nonmedullated nerve stuff; lesions of Recklinghausen's disease were present elsewhere

Local Overgrowth was the title Chandler (J 109: 1411 1937) gave to curious and gigantesque deformities of one or several digits, without other pathologic alteration. The part appears simply magnified. Worsley (BMJ 1 1411 1909) reported 2 such cases Gould and Pyle (Anomalies and Curiosities of Medicine Saunders, 1898 pp. 276 799) described the condition aptly Rogers (BritJSurg 16 684 1929) showed the lesions to be due to the presence of neurofibromatous tumors, which he was able to dissect out. Compare deep hemangioma with hypertrophy of an extremity (p 1117)





Fig. 1439A.—"Local overgrowth" of left thumb, index finger and middle finger (Chandler: J 109 1411, 1937.)
Fig 1439B —Cutis verticis gyrata. (Drs. Kessler and Kessler)



Fig. 1440.—Hereditary lymphedema of the hand.



Fig 1441.—Cutis verticis gyrata, the corrugated scalp of a man. (Dr A. M. Davidson)

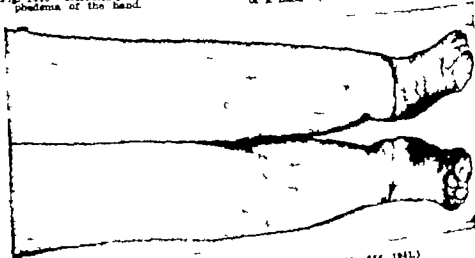


Fig. 144 —Milroy' disease. (Bloom NYSJM 41: 856, 1941.)

See Mason (SGO 64: 140, 1937) hand Fisl (PSMMC 10: 280, 1941) huge lesion of scalp; Good and Garb (ADS 47: 197 1943) scalp lesion, plus symmetric nevi of face, tuberous sclerosis and epilepsy; Westcott and Ackerman (ADS 55 [illegible], 1947) massive flabby tumors, 2 cases, back and axilla; Hedmann (AfDuS 187 [illegible], 1948), hemihypertrophy of face and neck; Oraviato (ActaOpath 27: 59 1949) eyelid cases; Stuart (BJD 62: 486, 1950) boy developed huge tumor of scalp.

Congenital Elephantiasis (Milroy's Disease)—The disorder is familial, present at birth, persistent and asymptomatic. One or both feet or legs may be involved. The hypertrophic tissue does not pit on pressure Milroy (NYSJM 56 505, 1892) observed this undescribed variety of hereditary edema and noted the white nodules which often accompany it. Meige (abs BJD 12 372, 1900) described its onset as occurring at various times after birth. The incidence of occasional attacks of swelling pain and fever in some of these patients was remarked by Hope and French (QuartJMed 1 312, 1907 1908) Milroy (J 91: 1172, 1928) reviewed the original family but found only 2 new cases, descendants of the original patient, among 30 siblings. Mason and Allen (AmJDisChild 50 945 1935) delimited the name Milroy's disease to cases which are both congenital and familial Cole in 1931 showed me a case of unilateral involvement in a Negro boy

See Nouma (AfPath 126 169 1931); Rosenberg (ADS 42 1112, 1940) 2 types: onset before birth and onset in adolescence, only the latter showing attacks of exacerbation; Bloom (NYSJM 41: 864, 1941), familial association with ptosis of eyelid, 6 cases in 37 sibs in 4 generations, Glaser (JPediat 24: 327, 1944) 2 cases not helped by pressure bandages Braham and Howells (BMJ 1 [illegible] 1948) case; Cook and Moore (J 147: [illegible] 1951) 5 cases in 2 generations, histologic change, dense fibrosis, not edema; Deocker and Gottfries (ActaMedScand 150 277 1954) young woman with pain and edema relieved by cortisone.

Cutis Verticis Gyrata is a harmless but unsightly abnormality of the scalp in which the skin is overabundant and thrown into waves and folds with roughly sagittal axes.

Alderson (ADS 6: 449 1922 26 1020, 1932) and Stratton (ADS 27: 892, 1933) reported interesting examples. In some of Alderson' cases there were inflammation and the history of severe injury and infection of a previously normal scalp. The case of Frenzl (DWehn 100: 18 1935) was associated with multiple hairy nevi of the tru k, so was thought to be nevoid. Fischer (AfDuS 141: 231, 1922) classified ( ) true cases representative of anomalous, at vistic reversion to the primitive folded scalp, and (b) cases simulati g this, but representative of (1) acut or chronic inflammatory disease, (2) anomalous or congenital hypertrophy of the connective tissue (3) neoplastic disease, including nevoid and neurofibromatous forms, nd (4) cases due to hypertrophying disease, such as acromegaly myxedema, leukemia and mycosis fungoides. Hammond and Ranson (ArchSurg 35: 309 1937) reviewed the subject in a detailed and scholarly manner a d accepted the existence of traumatic forms. The disord was acromegal c in the case of Benander (A taMScand 96: 156, 1935) and was benefited by roentgen treatment of the pituitary gland.

An osteod rmopathic syndrome was described by Leinward and Duryee (AnnIntM 19 1018, 1943) in which were featured thicke ing a d furrowing of the kin of the scalp forehead, face and extremities; elephantiasis of the long bones although the joints were normal; enormous hands, and nails shaped like a watch crystal; onset bef re age 20 years; and incidence not familial, limited to males. Normal sex power and mentality distinguished the condition from acromegaly

Plastic surgery has a good deal to offer in some of these cases, especially those representative of neurofibroma or cerebelliform nevus (q v) according to McConnel and Davies (AnnSurg 118 154, 1943)

See Unna (MonatshPrakD 14: 227 1907) origin of name; v Verres (abs BJD 21 [illegible], 1909), 10 cases, review Grönberg (ActaMScand 47 [illegible], 1927) acromegalic; Stratton (ADS 27 [illegible], 1933) bibliography; Brande and Greebeim (ActaD-V 15 [illegible], 1934), 67 Mongolian cases; Bejarano (Actasdermo-sif 27 [illegible], 1936); Toskov (BJD 49 [illegible], 1937) cromegalic; Keisler and Wieder (ADS 42 1092, 1940) 2 cases and review Jaeger (Dermatologica 86: 253, 1942) neuromatous histology

Dermatolysis was the name given by Wise and Snyder (JCutD 32 139 1917) to a disorder manifested by sessile doughy lumps disseminated in distribution. Dermatolysis and cutis hyperelastica (q v) are perhaps forms of Recklinghausen's disease with universal peripheral distribution.

They too are sometimes unil teral. The broad, lax, pend lous tumors which sometimes occur in Recklinghausen disease appear to consist mainly of fat and thickened skin and generally involv the face, as in Alibert's case in which the arms, axillae, but trunks and thighs were also affected. Crocke (Diseases of the Skin Blakiston, 2: 948,

Fig. 1443.—Dermatolysis (Wise and Snyder JCutD 32 139 1914.)



Fig 1444.—Multiple benign tumo like new growths of Schweninger and Buzzi. Freiter ADS 6 580 1922.)

1903) separated these examples of "fibroma pendulum" from cutis laxa (q.v.) which he restricted to apply only to the congenital cases presenting loose attachment of the skin without hypertrophy.

Curious examples have been recorded by Bielschowsky (DeutschArchKlinM 166: 96, 1930) involving the back and by Wiltschke (KlinWschr 45: 1014, 1932) involving the occipital and upper back regions of a newborn.

Multiple, Benign, Tumorlike New Growths of the Skin.—The Schweninger-Buzzi type of anetoderma is characterized by the occurrence of small, soft bean- to pea-size, circumscribed, whitish or bluish white, bladderlike formations, many of which can be pressed into a hollow in the underlying tissue like small hernias. The backs of the shoulders, arms, and trunk are the regions commonly involved. The lesions develop slowly with associated cutaneous atrophy. There are no symptoms. This type of atrophy is a clinical entity according to Chargin and Silver (ADS 24: 614, 1931). Pusey (JCutD 35: 582, 1917) whose patient's face and back were affected, found a dearth of elastic fibers suggestive, to him, of congenital defect. The disorder is a rare one, is thought by some to be a form of "primary macular atrophy." To me it appears to be a *forme fruste* of Recklinghausen's disease. Therapy is unavailing.

See Schweninger and Buzzi (International Atlas of Rare Skin Diseases, pt. 5, plate 15, 1891); Fox (BJD 4: 117, 1892); Crocker (Diseases of the Skin, Blakiston, 1903, p. 703); Pringle and MacCormac (ProcRoySocM 12: 21, 1919); Quinn (ADS 5: 149, 1922); Sweitzer (ADS 6: 539, 1922), review; Pardo-Castello (ADS 7: 446, 1923); Dowling (BJD 39: 55, 1927); Chargin and Silver (ADS 24: 614, 1931), review of macular atrophies; Tobias (ADS 29: 319, 1934), case; Kampf (ADS 33: 116, 1936), case; Butterworth (ADS 29: 832, 1934), onset at age 61; Feldman (ADS 33: 117, 1936), case; Hopkins (ADS 44: 744, 1941); Hollander and Schmitt (ADS 46: 414, 1942), unusual case; Hollander (ADS 63: 660, 1951); Grove (ADS 64: 402, 1951)

Cutis Laxa is featured by considerable variability in the amount of hypertrophy and degree of looseness, but the affected skin is usually thickened, more or less pigmented, and so loosely fixed to underlying structures that it hangs in baggy folds. The lesions are otherwise asymptomatic. The microscopic structure is that of neurofibroma.

In a review of abnormalities of distensibility of the skin, Carney and Nomland (ADS 56: 794, 1947) classified 5 groups: (1) dermatolysis of a diffuse, generalized hypertrophic kind; (2) congenital, generalized edema followed by diffuse dermatolysis; (3) the Ehlers-Danlos type of true cutis hyperelastica; (4) acquired atrophy, laxity and inelasticity which may follow inflammatory disease, and (5) "chalazoderma," wherein there is no prodromal disease and the loose inelastic, sagging skin is soft and thin, lacking the changes of senile atrophy but affecting young or middle-aged persons as exemplified by a case they described.

Bonnevie-Ullrich Syndrome.—Manifestations of cutis laxa in infancy may include swelling and tumefaction of the hands and feet, webbing of the neck, hypoplasia of various muscles and anomalies of their insertion, syndactyly, various bony deformities, retardation of growth and sexual function, anomalies of the cranial nerves and malformation of the nails (Carletti and Parenzan: Gio ItalD 93: 49, 1952). A syndrome characterized by the triad, webbing of the neck, cubitus valgus and infantilism was described on the basis of observation in 7 women, by Turner (Endocrinol 23: 566, 1938) who was unaware of Ullrich's earlier report. Ullrich (AmJHuman Genetics 1: 179, 1949) showed that Turner's syndrome is identical with that of Bonnevie and Ullrich. The review by Bartlow and Levin (BMJ 1: 890, 1955) is informative; they found reports of more than 100 cases, among whom the congenital lymphangiectatic edema stressed by Ullrich was actually rare. They thought the syndrome identical with that of ovarian agenesis.

Pterygium Colli Congenitum, wherein occur curious lateral folds of the neck associated with such endocrine anomalies as infantilism, obesity and amenorrhea, was described by Nageotte-Wilbouchevich (BullSocPediat 32: 683, 1934).

Gargoylism (Lipochondrodystrophy) attracted the interest of Cole et al. (ADS 66: 371, 1952) who described the typical sufferer as a short, ugly individual with large misshapen head, short neck, thick lips, large tongue, broad nares, depressed nose, large, low ears, wide interocular distance, emphysematoid thorax, and flexion deformity of the extremities. In their patient the hair was coarse and brittle and pronounced furrowing of the skin was noted in the shoulder and lateral thoracic regions, with ridges and induration. They thought the abnormality one primarily of collagenous tissues rather than of the fat or cartilage. A sex linked inheritance is not unusual.

Cutis Hyperelastica.—Synonyms include elastic skin, India rubber skin, dermatorrhexis, Ehlers-Danlos syndrome. The affection was first described by Meekren in 1682 (quoted by Crocker: Diseases of the Skin, Blakiston, 2









Figs. 1445-1448.—Cutis hyperelastica. Fig. 1445, upper left, shows hyperextensibility of skin at elbow in a 10 year-old girl, patient of Dr Paul Otto. Fig. 1446, lower left, the legs of this girl, showing scars and pseudotumors, one of which is ulcerated. Fig. 1447, upper right, shows a patient of Dr Everett S. Lain. Fig. 1448, lower right, is of Dr Lain's patient also.

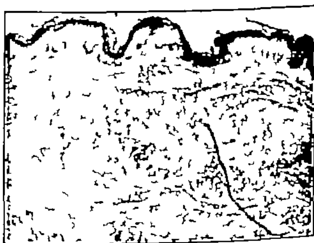


Fig. 1449.—Cutis hyperelastica, section of pseudotumor showing giant cells in whorls of myxomatous connective tissue, probably neurofibromatous. (Ronchese: Am J Dis Child 51: 1403, 1936.)

949 1908) The first patient recognized was one Georgius Albes, a Spaniard, whose peculiarity was limited to the right side of the body and enabled him to extend the pectoral skin to the ear the skin from the chin over the vertex of the scalp and the skin of the knee to a distance of 18 inches, from which it retracted without folds.

The skin is smooth soft, and seemingly somewhat thinned. It is ex traordinarily supple and elastic however and when a fold is drawn out from the body and released, it may return to its original position with an audible snap Laxity is especially marked about large joints. The deformity may be general or confined to certain regions.

THE EHLERS-DANLOS SYNDROME comprises all of the following (1) pronounced fragility of the skin and its vessels, so that even slight trauma produces hematomas and wounds that refuse to remain stitched; (2) the healing of these with the formation of pseudotumors (3) hyperelasticity of the skin; (4) hyperflexibility of the joints and (5) lineae distensae which with scars and peculiar molluscoid lesions on the exposed parts, are conspicuous features. Loose, pea-size spherules, firm to the touch but fatty under the microscope are found in numbers, especially in the loose skin of the extremities, where they sometimes undergo calcification (Holt AmJRoentg 65 420 1946) While these several manifestations collectively comprise the Ehlers-Danlos syndrome, *formes frustes* are more common

See Ohmann-Dumesnil (InternatMMag 1: 244, 1892) 1 case; Williams (MonatshPraktD 14: 490, 1892), histopathology by Unna; Danlos (BsocfrangD 19: 70, 1908); Pautrier (BsocfrancD 19 72, 1908) pathology in Da los patient, Gougerot and Hallos (BsocfrangD 24 162, 1926) Burrows (ProcRoySocM 6 1310 1932) illustration f Georgius Albes; Schulmann and Lévy-Coblentz (BsocfrancD 39 1252, 1932); Funabashi (ActaD-V 22 194, 1933) Tobias (ADS 30 540, 1934) case; Kals (ArDuS 171 155, 1935) cutis laxa; Ronchese (AmJDisChild 51 1403, 1936) constitutional mesenchymatosis, review Weber (BJD 48: 609, 1936) molluscoid pseudotumors; W ber and Aitken (Lancet 1 198, 1938), subcutaneous spherules Smith (JPediat 14 632, 1939) case; Tobias (ADS 40 135, 1939) 2 cases Skeer and Kaplan (ADS 42 456, 1940) case; Fritchey and Greenbaum (ADS 42 742, 1940) man and daughter; Coe and Sil ers (AmJDisChild 59 129 1940) incomplete dominant inheritance; Barber et al. (BJD 53 97, 1941) 2 familial cases, review Ross et al. (SemMed 49 887, 1942) brothers Ronchese (UCutRev 47 541, 1943); Cannon (ADS 50 231, 1944) case Brown (GlasgowMJ 27 7 1946) abnormalities in 19 of 47 sibs in 4 generation Turner (MJAustral 2: 165, 1949), case Pierard and Palmer (NZealMJ 48 7 7 1949) case, Johnson and Falls (ADS 60: 82, 1949) extensive genetic studies Ronchese (RhodeIslandMedJ 32 50 1949) case Rimgrose et al (ADS 62: 444, 1950) case Wallach and Burkhart (ADS 61 750 1950), case with congenital heart disease, review f associated anomalies; Pascher and Kanof (ADS 67: 314 1953) 2 cases, *formes frustes*, nd discussion of relation to hyper corticalism; Mc Illie et al. (BMJ 1 1311, 1955) man with spontaneous fract res, association of neurofibromatosis and osteomalacia.

OSTEODYSTROPHIA FIBROSA (POLYOSTOTIC FIBROUS DYSPLASIA)

Albright s Syndrome is a rare condition in which patchy pigmentation is associated with asymmetric cystic bone disease The original description was concerned with osteitis fibrosa, disseminated areas of pigmentation, endocrine dysfunction and precocious puberty in females, and 5 cases were reported by Albright et al. (NEngJM 216 727 1937) The distribution of the multiple bone cysts suggested a relation to nerve root or myotome systematization and the areas of pigmentation appeared to be in some way related to the osseous lesions. Hyperparathyroidism was not present. The patient of McCune and Brush (AmJDisChild 54 806 1937) had symptoms at the age of 2 years, and began to menstruate at that time Pathologic fractures are common.

While the disease is of unknown nature there are imilarities to xanthoma and to Recklinghausen s disease It occurs in both se es, it is now known, but gonadal dysfunction is seen only in females (Dockerty et al.: AIntM 75: 357 1945) Blood calci m is normal, and only scattered bones are affected, a distinction from hyperparathyroidism (Gorham NYSJM 43 415, 1943) Albright (JClinEndocrin 7: 307 1947) thought his disease not xa thomatous because blood cholesterol is not abnormal, a d the bone lesions progress only slightly clear spontaneou ly, nd are not radiosensitive. The segmental distribution of bone and skin lesions, which do not coincide in location, is against a metabolic eti logic agen cy The serum phosphatase level is high when the disease is widespread. He thought it not of the nature of neurofibromatosis because the latte does not i duce increased as well decreased bone formation in the same person or effect sexual precocity while the former does not run in families.

About half the cases show cranial bone changes and the skull participates in abnormality in all the severe ones, the deposits being maximal and located mainly at the base of the skull and in the face according to Windholz (AmJ Roentg 58 51 1947) It would seem that leontiasis ossea is actually a manifestation of extreme fibrous dysplasia One observes, on x ray replacement of

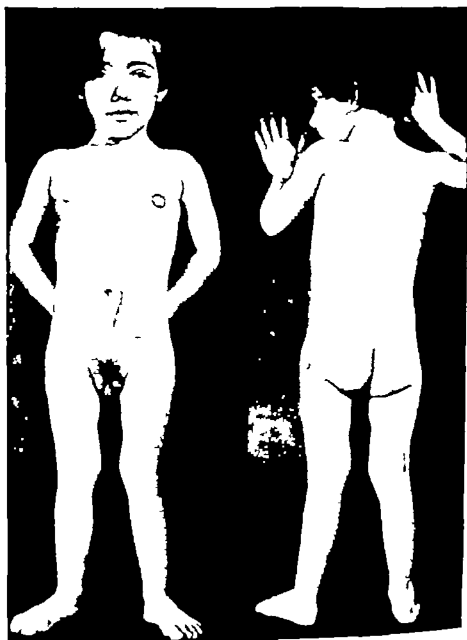


Fig. 1459.—Areas of pigmentation associated with osteitis fibrosa disseminata, endocrine dysfunction and precocious puberty in a 4-year-old girl who menstruated. (Albright et al NEngJM 216 727 1937)

the diploë by translucent material in which irregular poorly or completely ossified nonlamellated bone tissue may develop and show as radiographic densities.

Treatment is limited to palliation of symptoms correction of deformities and management of pathologic fractures if they occur

See Lichtenstein (ArchSurg 36 874 1938) 4 cases of polyostotic fibrous dysplasia; Coleman (BritJSurg ...) Ibrahim (ArchDisChild 14 181, 1939) onset followed icterus gravis; Coleman (Lancet 11 ... 1939) 11 261 708, 1939) male case autopsied Robson and Todd (Lancet 11 371, 1939)

cases reviewed; Maller (AmJDisChild 61: 890, 1941) 24 cases reviewed; Sternberg and Joseph (AmJDisChild 63: 748, 1942) case with exophthalmic goiter; Lichtenstein and Jaffe (ArchPath 33: 777, 1942), fibrous dysplasia, 23 cases; Lanigan et al. (IrishJMS 6: 71, 1947) case; Edit (J 135: 933, 1947); Vial (see YBD 1948, p. 264) male case; Warrick (JBoneJt Joint 31 B: 175, 1949) 4 cases of Lichtenstein' type, all males; MacRae (BMJ 1: 349, 1949) case.

DERMATOFIBROSIS LENTICULARIS DISSEMINATA AND OSTEOPOIKILOSIS

This rare disorder appears to be related to xanthomatosis, although it has long been confused with scleroderma, and may be a form of neurofibromatosis, according to Curth (ADS 30: 552, 1934). The papular fibrotic, symmetrically distributed lesions of her pa tie t were uniformly pea-sized, firm, slightly raised and of normal color and they under went no evolution. The eruption is usually papular sometimes purpuric. The eruption in conjunction with osteopoikilosis, the other element of the syndrome, is diagnostic. The combined osseous and dermal dysplasias were concisely reviewed by Weber (MedPract 221: 65, 1949). See Buschke and Ollendorf (DWchn 54: 257 1928); Po korny and Porkorny (DWchn 83: 157 1929). Compare systemic urticaria pigmentosa (p. 864).

TELANGIECTASIS

Telangiectases are dilations of small blood vessels. They are usually localized but may be widespread in distribution. They presumably result from the enlargement of pre-existing vascular channels. Telangiectases are symptomatic manifestations of a variety of dermatoses, including rosacea angiokeratoma morphea, roentgen dermatitis, erythema ab igne and xeroderma pigmentosum. They also result from the distortion provoked by any expand ing intracutaneous tumor. The lesions are seen as short tortuous, bright red lines beneath the epidermis. Telangiectasis of the thoracic skin overlying the attachment of the diaphragm is common its significance is unknown (Burrett and Scherf AmJMedSci 201 390 1941).

Telangiectasis may represent in some cases a *forme fruste* of nevus flammeus, localized systematized and even affecting the meninges and central nervous system, although such lesions present at or soon after birth tend to disappear spontaneously within 5 years. Weber (MP&Circ 210: 19 1943) discussed the varieties of telangiectasis, incl ding ruby spots, branching li ear varices of lower extremities, Osler s disease, volar erythema, congenital varicosities, hemangiectatic hypertrophy f the limbs (elephantiasis telangiectodes), the relation to purpura, telangiectasis macularis eruptiva perstans and its relation to urticaria and urticaria pigmentosa, metast tic carcinoma and angioma serpiginosum. Generalized telangiectasis was associated with infection of the sinuses and disappeared following the cure of the focus in a case of Ayres et al. (ADS 26: 56 1932).

A dilated capillary can readily be occluded by use of the electric needle (Guequierre ADS 44 259 1941).

Nevus Araneus (" **Spider Nevus** ") is a common type of bright red vascu lar dilation consisting of a central tumor of minute size surrounded by numerous capillary radiations. The little growths are usually solitary or few in number but they may be numerous, involving the face, trunk and limbs. Sometimes they are pulsatile being communicant with arterioles (Weber: BJD 50 31 1938).

Pulsatile Spider Nevi associated with hepatic disease especially with cirrhosis, were remarked by Williams and Snell (AIntM 62: 872, 1938). The appearance of tiny hemangiomatous tumors, with perhaps a minute quantity of warty epidermal hyperplasia overlying them, in association with pregnancy was reported by Davis (JObGyn 45: 667 1938) who thought they showed a predilection for the skin about the eyes, appearing especially in the fifth and sixth months. They may disappear after parturition.

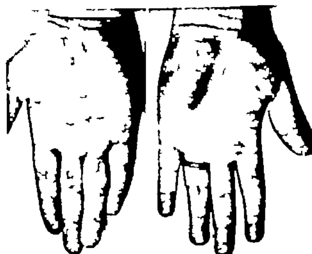
Arterial spiders and related palmar erythema (q v) seen in chronic alcoholics, persons receiving estrogenic hormone therapy and pregnant women, suggested to Bean (Sci 204 251 1942) that the lesions may result from intox ication of the endothelium of minute vessels by abnormal metabolism of 17 ketosteroid substances. Bean (AmHeartJ 25: 463 1943) found spiders associated with 8 of 11 cases of familial palmar erythema and observed that they waxed and waned concomitantly with the redness of the volar skin.





Fig. 1451.—A vascular spider elevated and manifesting readily palpable pulsation. (Bean et al. [illegible] 88: 739, 1949.)

Fig. 1452.—Typical large vascular spiders, the lower one of which has been covered with oil to reveal the vessels radiating from the center. (Dr. Wm. B. Bean.)





Figs. 1453–1455.—Varieties of telangiectatic erythema of the palm. Fig. 1453, left, shows mottled erythema representing exaggeration of normal mottled pattern. Fig. 1454, middle, shows the [illegible] which is most marked on the hypothenar eminence, with lesser involvement of the thenar eminence, the palm between the pads near the metacarpophalangeal junction, and the finger tips. Fig. 1455, right, shows sharply localized palmar erythema of pregnancy which subsided completely after parturition. (Bean et al. [illegible] 111: 127, 1949.)

Cutaneous arterial spiders were clearly distinguished from telangiectases by Bean (Med 24: 243, 1945) in a monographic article in which the relationship of estrogen and hepatic disease to spiders and palmar erythema was elucidated. In cirrhosis of the liver diminution of steroid metabolism results in increased estrogen levels, and these result in spiders, thought Lloyd and Williams (AmJMed 4: 315, 1948)

According to Bean et al. (SGO 88: 739 1949) vascular spiders complicating pregnancy were first noted by Corbett (BJD 26: 200 1914) and palmar erythema in pregnancy by Feldman (ADS 39: 784 1939) Spiders have been found in about 67% of white women and 10% of Negro women during pregnancy appearing as early as the second month and through the fifth month increasing slowly in number and size until term. About 75% of them disappeared by the seventh week after delivery Palmar erythema appeared in about the same proportion of white women but in some three times as many colored women as spiders did, but the timing was similar Liver function tests showed no abnormalities.

I have seen them appear following overdosage of vitamin concentrates, substances rich in carotenoid pigments, and homogenized milk. Trihexyphenidyl given for Parkinsonism induced the development of numerous pulsatile spider angiomas on the face, neck and chest in a patient seen by Holt (NEJM 49: 318, 1953); the lesions disappeared after withdrawal of the drug.

Capillary microscopy was applied to the various vascular dilations of the skin with interesting observations by Redisch and Pelzer (AmHeartJ 37: 106 1949) Simple telangiectases showed no pulsation and blanched when either end of the vessel was compressed. They contained no active blood flow and did not undergo constriction when epinephrine was injected locally Sometimes such lesions were branching Arterial spiders exhibited 3 types of vascular structure: the central "body," the radiating "legs," and the bright red capillary flare between the radiations of the dilated minute channels. Active blood flow took place in these. Pressure on the central spot blanched the radiations, which apparently were passive channels. While epinephrine blanched the flare it did not blanch the radiating vessels. Spiders did not disappear they noted, until several hours after death.

See Chlorschi (WienKlinWchr 63: 478, 1940) spiders in 22 of 41 cases of hepatic cirrhosis; Walsh (ADS 47 455, 1943) alcoholic cirrhosis; Bean (JLabClinM 30: 190, 1945), infrared photography does not show arterial spider or telangiectases of Osler' disease, but venous lesions show Brick and Palmer (J 155 8 1954) In cirrhosis, spiders more common if esophageal varices are present.

Venous Stars, representative of engorgement of the ordinary drainage system of the small veins in the skin, becoming visible when these are subjected to prolonged increase in intravascular pressure are to be distinguished from arterial spiders (Bean TransAssnAmPhys 64 100 1951) They become *remarkably developed when there is obstruction of the superior vena cava*. Venous ectasia in the form of macular groups of linear purplish blue vascular channels on the sides of the thighs or legs is a common complaint of otherwise healthy young women who are concerned with their appearance. They seem generally to have no consequential significance and are not as a rule associated with conspicuous varicosity Obliteration of these veins is accomplished by injecting bubbles made by vigorous shaking of a 5% solution of *sodium morrhuate within a syringe before injection* A 26 gauge needle is used for entering the small venules, which must be done carefully because of the fine caliber of these vessels. The injected bubbles ascend into the ramifying tributaries. On withdrawal of the needle the region should be massaged in order to bring the venule walls into contact with the solution. Some of the smaller vessels can be obliterated by electrolysis or the high frequency current. The electrolysis needle is inserted and withdrawn with the current on, in contrast to practice in removing hairs, where the current is on only while the needle is at the site of action (QMN J 155 946 1954)

Papillary Varices (DeMorgan Spots Cayenne Pepper Spots) are ruby colored, pinhead to pea-size rounded, vascular tumors which develop especially on the trunk of middle-aged or elderly persons. The lesions are bright red because they are filled with fluid blood, but sometimes they become thrombosed. In these papular lesions, the elastic tissue is greatly diminished in the papillary and subpapillary layers of the corium but this is not due to senile atrophy in the spider nevus there is a single-layered endo*thelial sheath* comprising an ectasia in the subpapillary layer according to Beck (AfDuS 175 484 1937) who called them senile angiomas. Statistical study of them by Murison et al. (BMJ 1: 63 1947) revealed that the incidence

rises with age from 5% in adolescence to 75% in individuals of 70 years there was no relationship with malignancy They are readily removed by electrocoagulation. See Weber and Handley (BMJ 1 864 1947)

Capillary Varices of the lips are common. Circular smooth, purplish in color situated immediately beneath the epidermis, generally of the lower lip these soft, compressible lesions are benign and persistent. They are readily eradicated when this is done largely for cosmetic reasons, by removing the entirety of the external covering with the cautery and applying the electrocoagulator to the base.

Livedoid Telangiectasis.—See Hemangioma, macular

Francke's Striae.—Telangiectases of red wine color unilateral or bilateral, near the seventh cervical spine were described under this title by Allmenti (GiorTisiol 11 14 1937) They are said to occur in 45% of patients with pulmonary tuberculosis. See Striae atrophicae

Hereditary Hemorrhagic Telangiectasis (Osler's Disease) is an inherited anomaly affecting either sex (Osler BullJHH 12 333 1901) Telangiectases and angiomas occur on the face tongue nasal septum, buccal mucosae and elsewhere, including the internal organs. Rupture of these red or purplish





Fig. 1456.—"Cayenne pepper spots" about left breast.
Fig. 1457.—Telangiectases in the superficial dermis, as seen histologically

vascular dilations may give rise to hematuria or to hemorrhages which may necessitate transfusions (Stellar NEngJM 226 336 1942) Transmission is by either sex (Goldstein AIntM 48 836 1931) and an unusually large sibship was reviewed by Alban (NoWM 40 86 1941) involving 6 generations. Pardo-Costello and Farinas (ADS 39 1025 1939) confirmed the histologic finding of elastic tissue deficiency

Williams (ADS 14 1, 1926) laid to rest the misapprehension that the condition is rare Routine examination of the mouth will reveal many persons with purplish telangiectases along the under sides of the tongue Few who are affected suffer hemorrhages although they are predisposed to them. Generalized, disseminated, pinhead size cavernous angiomas did not involve the mucosae of the man reported by Archer (Lancet 1 595, 1937) but the condition was inherited and the patient suffered hemiplegia at 30 years of age

In angiokeratoma of the scrotum one often finds telangiectases in the mouth, angiokeratoma of the scrotum is a manifestation of Osler's type of structural impropriety

The Rendu-Osler-Weber disease is characterized by bleeding telangiectases and family history Nosebleed is the usual presenting symptom, and telangiectasis is rarely seen before puberty Inheritance is usually as a simple dominant, but a generation is sometimes skipped. A historical review and genealogic charts of 60 families were given by Garland and Anning (BJD 62: 289 1950); among 1451 affected persons in 15 families, 03 were females and the defect was transmitted by males and females in about equal proportions.

The sweat duct orifices were the location of multiple small, cavernous hemangiomas which were peppered over the trunk and extremities of the unusual patient of Archer (Lancet 2 503 19—) The lesions were of pinhead size. The tongue was not involved, but the young man suffered attack of hemiplegia.

Bleeding was controlled by giving rutin, 40 mg t.i.d., in the case of Kushlan (Gastroent 7 109 1946) A slightly larger dose was helpful in the patient of Markoff (SchweizMWchn 78 984, 1948) The flavone substance stopped nosebleeds in the case of Cope and Grover (JID 10 39 1948) and in the little girl reported by Klauder (ADS 57 417 1948) It was of no benefit in cases of Petch (BMJ 2 785 1948) or of Ashby and Bulmer (BMJ 1 1059 1951) Snake venom is without value (Peck et al. ADS 35 831 1937) Accessible lesions are easily destroyed by electrocoagulation.

See Rendu (BocmedHôpParis 13 731 1896 GazHôp 69: 1322, 1896); Steiner (AIntM 19: 194 1917), review Goldstein (AI tM 27 102, 1921; 48 836, 1931 ADS 26 282, 1932 BMJ 1 721, 1936) reviews, bibliography cases Becker (ADS 14 387 1926) clinical study; Foldvari (ActaD-V 14 437, 1933) 207 cases since Osler description Houser (AOtol 20: 438, 1934) Pearlman (AOtol 23 287 1936) treatment of nasal mucosal lesion by adjacent injection of 5% quinine and urethan; Kostner (KlinWchn 14 712, 1935) bleeding from nail beds; Fingerland and Janousek (ArDuS 178: 84, 1938), histology; Hottenroth (ArDuS 178: 482, 1939) Tasham (AnnIntM 13 836, 1939) 5 generations McDonough et al. (PMMC 15 591, 1940); Griggs and Hacker (AmJDigDis 8 344, 1941) bleeding from gut; Singer and Wolfson (J 126: 84, 1944) 16 of 48 sibs Cappon (BMJ 1: 440, 1948), 4 generations; Garland and Anning (BMJ 1 700 1950) 3 more families, association of arteriovenous aneurysm of lung Hardt et al (Gastroenterol 28 78, 1955) massive gastrointestinal hemorrhage.

HEMANGIOMA

Symptoms.—A hemangioma is a localized hyperplasia of blood vascular tissue The lesions may involve the dermis the subcutaneous tissue or both. They range greatly in size but are usually reddish or purplish in color with a flattened surface slightly elevated above the sureca Vascular nevi may be separated into 2 groups (1) macular or slightly elevated tumors composed of a superficial plexus of dilated capillaries angioma simplex, nevus flammeus, port wine stain and (2) hypertrophic, bulky angiomas hemangioma cavernosum.

Hemangiomas are congenital or appear shortly after birth. They range in diameter from a millimeter to many centimeters. The lesions may appear anywhere on the skin or in deeper tissues. They may be solitary, few or many in number over 300 were present in the newborn reported by Digonnet et al. (BsocfrançD 46 162 1939)

Macular Hemangiomas may involve small or large areas. The extensive cases have a distribution suggestive of that of the sympathetic nerves. They are sometimes arranged in the form of a nevus unius lateris, such as the patchy example on the side of the face of a child reported by Oliver and Bluefarb (ADS 46 315 1942) The nevus flammeus observed by Traub (ADS 39 752, 1939) did not appear until the subject was 23 years old, and it was after severe trauma that spotty redness developed in the trigeminal area of a man seen by Fegeler (ArDuS 188 410 1949) A basal cell carcinoma developed within the lesion, probably a mere coincidence in the case of Schonberg (Ohio SMJ 35 850 1939) I have seen such a case Multiple lesions occurred in several members of 4 generations of a family reported by Shelley and Livingood (ADS 59 343 1949) See also hemangioma with nervous system involvement.

Nevus Flammeus Nuchae (Unna's Nevus) is one of the commonest congenital defects of the skin. Appearing at birth on the nape of the neck, it generally has its long axis vertical and is roughly symmetrical. It may be only faintly pink. The edges are lacy (Corson: AmJMedSci 187 121, 1934)

Superficial Fading Hemangiomas.—Diffuse flat pale red areas over the nucha occiput forehead or abdomen are often seen at birth. The color is intensified when the child cries. This type usually regresses spontaneously without treatment more or less completely (Kaessler J 110 1644 1938)

Livedoid Telangiectasis.—Hemangiomas of circumscribed extent and superficial location composed solely of serpiginous capillary channels separated by appreciable quantities of apparently normal skin, have been described by

Hess and Kerl (DZtschr 33 125 1921) and Williams and Goodman (J 55 955 1925) The lesion, as in a case I have seen involving the arm of a boy may simulate chronic roentgen dermatitis but the texture is not altered, there are no keratoses, and the margin is sharply demarcated. The condition is





Fig. 1458.—Macular hemangioma.
Fig. 1459 —Cavernous hemangioma of the scalp in an infant.





Fig. 1460.—Macular hemangioma, "port wine" mark. Irremediable
Fig 1461 —Typical scar of cavernous hemangioma treated by x-ray during infancy 10 years previously as good a result as may be expected.

simply macular hemangioma incompletely faded. Generalized telangiectatic livedo was seen by Neumark (ActaD-V 19 316 1938) in a girl 3 years old whose redness faded during the next 8 years. Telangiectatic and pigmented macules involved the skin and conjunctivae of a child with symptoms of cerebellar disease in a bizarre case of Louis Bar (abs ADS 46 890 1942)

Cavernous Hemangiomas develop slowly and may cause serious alteration hypertrophy or destruction of the tissues by altering the blood supply They may be small at birth and gradually increase to a certain size where they re-





Fig 1442.—A cavernous hemangioma which did not undergo spontaneous resolution in childhood. (Dr H P Kessler)

Fig. 1443.—An unusual hemangioma. (Dr S. T Hagan.)



Fig. 1444.—Hemangioma near medial malleolus since infancy recently injured, now ulcerative. (Dr D. E. H. Cleveland)

main stationary or spontaneously undergo involution (Lister Lancet 1 1429 1938) leaving white or mottled atrophic scars. One cannot predict which lesions will disappear Purplish, soft and compressible, they bulge when the

child exerts himself. They may rupture if ulcerated, so as to bleed dangerously Large cavernous tumors are sometimes built about arteriovenous aneurysms and are audible (Seeger Surg 3 264 1938) Multiple cavernous hemangiomas may be disseminated and are sometimes systematized (Oberreit DZtschr 73 75 1936 Kelly ADS 43 418 1941) Other structures may be greatly altered by the presence of the vascular tumor so that elephantiasic deformity exists (Sayer and Silver ADS 61 868 1950) A small skin lesion may be the sole external manifestation of a large subcutaneous hemangioma





Fig. 1465.—Hemangioma, slowly progressive over a period of 40 years, unresponsive to roentgen therapy Histologically the tumor seemed benign.

Fig 1466.—Systematized hemangioma, affecting left lower extremity of a man. Despite resemblance to Kaposi sarcoma, this remained unchanged for 30 years. Such case was reported by Volrwinkel (DWchn 166 128, 1938) as Naevus varicosus et osteomatosus which he presumed to be related to Kaposi's disease

Strawberry marks are common abnormalities. I tell anxious parents at the time of the first consultation that the tumor is nobody's fault it does not represent something done that should not have been done or something not done that should have been done (mothers have a way of blaming themselves for these imperfections) The tumors are for practical purposes, never malignant A better therapeutic result is generally obtained than the parents expect In only exceptional cases is the infant's welfare significantly damaged by the presence of these lesions. They were found in slightly over 1% of both white and Negro infants by Pratt (ADS 67 302, 1953)

A number of syndromes depending for their characterization on the location and extent of hemangiomatous deformity have been segregated, including the Sturge-Weber (with anomalies of the brain) the Klippel Trenaunay (with varicosities and bone changes) and the Parkes Weber (with macular angiomas and bony hypertrophy); these were all classed as hamartomas by Graul (Hautarzt 4: 510 1953)

Deep and Skeletal Hemangioma.—Involvement of the knee joint was described by Bennett and Cobey (ArchSurg 38: 487 1939) who collected 29 such cases. Lesions of the hands and feet were discussed by Oughterson and Tennant (Surg 5: 73, 1939). Primary involvement of the skeletal muscles was observed by Shallow (AnnSurg 119: 700 1944) pharyngeal lesions by Lillie and Heck (PSMMC 23: 396, 1948) intestinal hemangiomas by Haycock and Dickinson (BMJ 1: 620 1951). The rupture of a liver lesion resulted in fatal hemorrhage in a newborn seen by Kissinger et al. (OhioMJ 36: 383 1940)

Multiple hemangiomas associated with chondromata, Kast s syndrome, were noted by Carleton and Robb-Smith (BJD 51: 92, 1939) theirs was the fourteenth case since Kast s description in 1889. Dyschondroplasia with hemangiomas, described as Maffucci s syndrome by M llias and Livingood (ADS 63: 478, 1951) is commoner in males, has it onset before puberty is asymmetric and usually unilateral in distribution, and causes susceptibility to fractures.

Klippel Trenaunay osteohypertrophic varicose nevus i a unilateral abnormality as a rule, wherein the affected limb i larger lo ger and warme than the normal one. It is to be differentiated from Milroy's disease.

Nervous System Involvement.—Widespread involvement of the face is associated with like involvement of the meninges, and the ciliary body may be affected so that glaucoma results (Dunphy: AmJOphth 18: 709 1935 Goldberg ADS 53: 503, 1946). Spontaneous intracranl l hemorrhage has been noted in association with trigeminal nevi (Cushing: J 47: 178 1906). Nevoid amentia is a name applicable t a syndrome of cavernous nevus in the fifth nerve distribution vascular buphthalmos of the eye on that side, a gl oma of the pia, and homolateral hypoplasia of the cerebrum, with atrophy and calcification (Sturge-Weber disease Massey and Miller: BMJ 1: 832, 1939 Anderson: Yale JBiol 18: 103 1945). Contralateral Jacksonian epilepsy and hemiparesis commonly accompany the mental retardation in such cases. Auditory hallucinations may occur when the temporal lobe is affected.

The spinal cord a d skin were inv lved in the same metameric segment in the patient of Cross (ANeurol 58: 359 1947) the sixth such case on record. The cervical lesion caused weakness of the extremities on that side and a compressi g cord lesion was found t operation. Angioma of the spinal cord resulted in fatal hemorrhage after an injury in the case of Gilbert (BMJ 1: 468 1952)

In deep lesions, even those affecting the brain or cord, x ray therapy may prove helpful or even curative (Karshner et al.: ArchSurg 39 94., 1939)

See Sturge (ClinSocTransact 12: 162, 1879); Kalischer (DeutKlinWchn 34 1059 1897) first autopsy; Ballantyne (BritJOphth 14: 481, 1930) glaucoma; O'Brien and Porter (AOphth 9 715, 1933) glaucoma; Brinton (ProcRoySocM 26 346, 1933) Brushfield-Wyatt syndrome, trigeminal port wine lesion with calcified gioma in cerebral hemisphere; Weber (BMJ 1 788, 1936) extensive unilateral ascula nevi with brain involvement Johnson (J 110 119 1938) scalp nevus and epidural tumor of same segment Evans and Evans (BritJOphth 23 93, 1939) nevus flammeus and optic trophy; Haines and Pumphrey (AmJDisChild 61 457 1941), Sturge-Weber syndrome; Cohen and K y (AmJDisChild 62 604, 1941), case; Ironside and Hill (JMentSci 87: 431 1941) case Poble and Clark (UCutRev 49 381, 1948) lesions of bones, subcutaneous tissue and central nervous system, responsive to x ray; Lichtenstein and Rosenberg (Neuropath 6: 369 1947) Sturge-W ber Dimitri disease; Worster Drought (BMJ 2 414, 1948), Sturge-Kalischer Weber syndrome; Bluefarb (ADS 59 531 1949) case and review; Pritchett (AfDuS 194 133, 1953), 53 cases of Klippel Trenaunay-Weber syndrome reviewed; Lichtenstein (ArchNeurol 71 291 1954) neurocutaneous hemangiomatosis; Sylen and Karavitis (TSMMC 29 282, 1954) neurosurgery in angiomatous malformation of cerebrum; King and Schwarz (AJath 94 742, 1954) 8 cases, Sturge-Weber type; Bil er (J 156 1082, 1954) pathologic studies of vascula tumors of the central nervous system.

Hemangioma and Retrolental Fibroplasia.—Retrolental fibroplasia causes blind ess of about 700 children a year (Reese and Blodi: NYSJM 53: 2869, 1953) a d is characterized histologically by angiomatous tissue budding from the retina into the vitreous body and g hemorrhage, orga ization thereof and scarring. The association of this con dition a d cutaneous hemangiomas, especially in premature infants weighing from to 4 pound at birth, was noted by A drews nd Domonkos (ADS 68: 320 1953). They called attention to the parallel f the fibroti disease f th eye d hemangioma, with respect to their early appearance soon afte birth th ctive d progressive phase and the regressi d cicatricl l phase. They observed 20 skin hemangiomas in 80 prem ture f ts, and eye disease was present i fourth of them, whereas they found only 23 hema giomas in 707 prematures in whom eye disease did not develop. Premature inf nts with hem ngioma need frequent examinations by the ophthalmologist.

Etiology and Pathology.—The cause of hemangioma is not known. The myth of prenatal maternal impressions has long been in the discard. Amusing case histories were recounted by Turner (De Morbis Cutaneis, London 1726 p. 183). Their presence is no one s fault, a fact which comforts and should be conveyed to the mother. According to Kaessler (J 110 1644 1938) Ribbert by injecting the vessels, showed that they have few or no lateral anastomoses injected material flows freely through the efferent and afferent chan nels. Yamada (JapJD 40 109 1936) discovered that hemangioma tissue does not wheal with histamine and he believed that this indicates local aplasia of vasoconstrictor nerves. Histologically hemangiomas are growths made up of dilated capillaries, endothelium and connective tissue. The endothelium is closely packed and, in parts, solid and without channels.

Treatment.—The earlier treatment is undertaken, the better (Bailey and Kiskadden Radiol. 38 552 1942) The *lesions* sometimes undergo *spontaneous* obliteration, so that Anderson (JPed 25 148 1944) would not treat them until after the age of 5 years, believing that they always stop growing by 1 year of age; see confirmatory views of Ronchese (AmJSurg 86 376, 1953) Wallace (BritJPlastSurg 6 78 1953) van der Werf (abs J 155 1017 1954) Bivings (JPediat 45 643 1954)

Since some lesions grow to large size rapidly and since in my experience, lesions *treated early* commencing in the first *few weeks of life*, generally do *very well*, and since *I cannot predict* which lesions will involute spontaneously and which will not *I strongly* urge early treatment and deny the wisdom of waiting *Cases of persistence* were presented by McCuistion (ADS 69 219, 1954) *On involution*, spontaneous or forced, the result is cicatricial, resembling *the scar of* a scald, and is sometimes hairless. Parents should be so advised before *treatment* is undertaken.

Whether the favorable effects should be ascribed solely to therapy or to the initiation of spontaneous sclerosis thereby is debatable *but that favorable* effects occur is not.



Fig 1447—Capillary hemangioma. (Dr Fred Weidman.)

The electric needle serves for eradication of small growths.

Some lesions can be coagulated beautifully by means of solid carbon dioxide (Wrong CanadMAJ 41 571 1929) Solid carbon dioxide is particularly suited for *superficial bulging* lesions. Those with deep purplish, subcutaneous extension do not react so favorably although CO will *eliminate* the bright red part on the surface. When the lesion is spotty consisting of groups of small red tumors, CO_2 does well It is applied with firm pressure for about 6 seconds, using an applicator that covers the lesion with a margin of 2 or 3 mm. The resultant burn may be expected promptly to blister and the bleb will break within a few hours. It is then treated with generous applications of talcum powder so as to obtain a dry scab. The infant is hurt *only* briefly and will stop crying *within* 2 minutes. The refrigeration wound is entirely *painless* unless it becomes secondarily infected in which case tetracycline *ointment* is a suitable application. It heals in 2 or 3 weeks. Any residual *hemangioma* may later be retreated with CO_2 or some other agent CO_2 is *my first* choice in suitable lesions. Even in large tumors consisting of

a central red, bulging portion surmounting deep hemangioma not accessible to CO_2 I use the agent on the red part early and continue later therapy with x ray In many cases a one-visit completely satisfactory cure is obtained.

X ray therapy is generally my second choice although for some lesions it is first. The dose is from 300 to 400 r at 120 KV sometimes with 1 mm.Al. This dose is repeated each 4 to 6 weeks until the total dose approaches 1200 to 1500 r Such a schedule may be applied to lesions of the scalp as large as 3 cm. in diameter with the expectation that hair growth will not be damaged. I no longer use radium, for the intensity of its effect is shallow and homogeneity of dosage in depth is impossible to attain with ordinary applicators.

In giving x ray treatments, which require from 30 to 90 seconds, the infant must be forcibly restrained for the necessary time. I use the help of the parents, who will not be damaged by a small amount of stray radiation. Shielding should allow the lesion and a margin of about 5 mm., including the entirety of the subcutaneous portion to be irradiated.

When a lesion is extensive, a carefully prepared map is made and specific parts of the whole are individually irradiated. The results are often surprisingly good. After from 3 to 5 treatments of 300 r have been given in a period of 6 or 8 months, regression is nearly always satisfactory

A standardized technic for the use of radium by surface application was worked out by Andrews (JID 10: 95 1948) Andrews et al. (AmJRoentg 67: 273, 1952) presented the results of extensive experience with the method as used t the Presbyterian Medical Center. This report was concerned with 1229 cases, of which 321 were macular or spider nevi, 892 were simplex or cavernous, and 26 were lymphangiomas. Some 90% were present at birth and began as tiny red spots which grew sometimes to huge size while misguided pare ts and physicians waited for them to regress spontaneously Treatment, Andrews et al. were convinced should commence at an early age.

A full-strength applicator (5 mg Ra per square centimeter) was sed with 2 mm. brass filtration. This was held snugly against the lesion for from 3 to 3½ hours, and such treatments were repeated at intervals of 3 months for a total of 3 or 4 applications, fewer proving sometimes sufficient. When 4 treatments had been given, no more were, and in the vast proportion of cases the result was very satisfactory What was left of lesions which had not been cured by 4 treatments we t away in time.

Surgical methods include excision, plastic surgery and the injection of sclerosing agents. These are suitable especially for large and extremely thick lesions, which are not amenable to x ray or CO_2 Surgical methods are generally preferred by surgeons Gerlach (BeitrKlinChr 159 129 1934) reported 84 cases so managed. Figl (AOtol 24 271 1936 PSMMC 12: 437 1937) assessed radium as the most effective agent in hemangioma of the face in children; electrosurgery he thought best in many cases of cavernous lesions in the adult. If the lesion had been previously treated unsuccessfully with radium, he recommended excision and grafting his choice was usually between radium coagulation, and excision and it generally depended on the location, size and cosmetic result he thought obtainable

The methods of treatment using sclerosing agents were reviewed by Kaessler (J 110: 1644, 1938) who preferred 20% solution of quinine dihydrochloride and urethan diluted with an equal amount of 2% procaine hydrochloride with epinephrine. Using a 26 gauge needle, he made radial injections from a central point with a 0.5 cc. tuberculin syringe placing 0.1 t 0.2 cc. of the sclerosing agent in each spot. The area would blanche and droplets were placed so that blanched areas became contiguous. It might be necessary to repeat after a month, and 1 to 6 treatments might be necessary Kaessler claimed good results in 44 lesions in 30 patients of ages ranging from weeks to 3 years, though he admitted the dange of slough. He claimed results equal to those obtainable with radium.

The insertion of small magnesium spikes, t set up an inflammatory reaction with the ensuing formation of fibrous bands, is a m thod suggested by Sonntag (ErgebChir 8 1, 1914) Excellent results can be obtained by inserting elongated, V-shaped particles cut from a strip of photographer's magnesium tape, the edges barbed to prevent premat re expulsion from the tissues. Absorption occurs in about one week.

All methods of treatment depend on the cicatricial obliteration of vascular channels; they all produce scar and a child s parents must know this before treatment is begun. The treatment of infants carries with it onerous medicolegal responsibility and is not to be entered into lightly for the patient may after

reaching 21 years of age exercise the right to claim malpractice against the estate of a physician who has died of old age since rendering the medical care in question The use of radiotherapy in any form in the vicinity of the eyes is especially hazardous.

In macular lesions, if the color does not disappear on diascopy it will not under radiation therapy Port wine stains cannot be treated successfully and in general should not be tampered with They may perhaps be hidden by tattoo (q v) and can be concealed by cosmetic preparations.

The technic of tattooing for the purpose of hiding the lesions was discussed by Conway and Docktor (SGO 84: 866, 1947) Conway (NYSJM 48 *040, 1948; J 152 666, 1953), and Leshin (ADS 68: 208 1953) It requires especial skill and the results are not often satisfactory

In treating port wine stains, I do not approve the use of grenz ray therapy (Kuh Strahlentherapie 57: 510 1936; White: IllMJ 76: 449 1940) or radium (Kaplan UCutRev 44: 397 1940) A method which appeared to have promise was described by Johnson (Acta ChirScand 95: 275 1947): under local anesthesia he rubbed off the superficies of the lesion with sterilized sandpaper and controlled bleeding with pressure bandages. Skin planing as used in the treatment of acne (q.v) might be applicable but one does not read many professions of success with this measure.

An extensive nevus in which admirable results had been obtained by tedious and meticulous fulguration was exhibited by Klauder in 1926.

Ultraviolet light therapy has been advocated (Clark: TherapGaz 40: 31, 1916), and one used to read reports of brilliant results following the use of the water-cooled quartz lamp. Eastland (SouthMJ 2 : 802, 1934) found ultraviolet of little practical utility MacCollum (AmJSurg 29: 33, 1935) claimed improvement or cure of 80% of 36 port wine nevi with blistering doses of water-cooled quartz mercury vapor arc light. Sutton, Sr., denied its value.

The child with an extensive macular hemangioma should generally speaking be taught by its parents to disregard the abnormality Friends soon no longer see it, and adult strangers give it but a passing glance If the disfigurement carries with it no emotion, it does the individual no harm (except the extensive unusual cases complicated with deep tissue, ocular or nervous system defects) Anything done to a normal macular hemangioma makes it look tinkered with. It may be hidden with Covermark.

See Hemiatrophy, Telangiectasis; Sarcoma of Kaposi. Fox (UCutRev 40: 3?8, 1935) treatment Fiml (BMJ 2, 671, 1935) treat early radium preferred Geschickter and Keasbey (AmJCanc 23 568, 1935) 670 hemangiomas, malignancy rare, hemorrhagic basal cell carcinoma (q v) Möller (Strahlenther 59 602, 1937) x-ray in small doses Andrews (ADS 37 573, 1938) radiation methods Basasch (Strahlenther 63: 406, 1938) interstitial radium; Vohwinkel (DWchn 106 135, 1938) varicose, angiomatous, unilateral nevus Touraine and Duperrat (AnndeD 7 545, 1930) types; Young (JPediat 14: 671 1939) excision; Strandqvist (ActaRadiol 20 185, 1939) gamma ray treatment at Radiumhemmet Ward and Crampton (J 114 2060, 1940) radium Hodges et al. (Radiol 36 708, 1941), contact x ray Edwards (SouthMJ 34 717, 1941) 107 cases, do not procrastinate in treatment Spencer (AmJRoent 46 220, 1941), 137 cases followed, radium or high-voltage x ray recommended; Simpson et al (IllMJ 79: 21 1941), radium surface applications; Apthomas (BritJRadiol 15 42, 1942) radium plaques, contact irradiation; Kerr (Radiol 39 183, 1942), 96 cases treated with radium and with contact x-ray little difference in results, Pfahler (Radiol 46 159, 1946) types of nevi and needle technics, let portwine stains alone Costello (Pediat 4 825, 1949) 22 cases followed nevi and treatment appropriate for each Ronchese (ADS 60: 717 1949) Diethelm (Schw J 10 to 15 years after radium total dose of about 75 mg hr no ill effects; Diethelm 26 years previously 140 776, 1952) cancer in scar from x ray treatment of hemangioma 26 years previously each 3 or 4 weeks, Bowers (BMJ 1 121, 1951) thorium X in alcohol, 1,500 e.s.u./ml. applied each 3 or 4 weeks, good results in some macular cases. Thompson and Shafer (J 145 369, 1951), arteriovenous aneurysms Goldsmith (BJD 63 163, 1951), multiple lesions Aiken (BMJ 2 1122, 1951), diathermy Brain and Calnan (BJD 64 147 1952) treatment Brown and Fryer (Plastic Reconstrsurg 11 197 1953) plastic surgery, Wilson (SouthMJ 46, 406, 1953) 200 cases treated by low oltage x-ray Church and Sneddon (BJD 66: 244 1954), hereditary cavernous hemangiomatosis, 8 cases in 3 generations appearing at puberty Rigdon (Cancer 15, 7 1955) methylcholanthrene topically applied producing hemangiomas in skin of white Pekin ducks, lesions regressing spontaneously histologic study of regression; Fitt (BMJ 2 1955) varieties of hemangiomas.

Venous Varix of the neck was remarked by Barber (BMJ 2 939 1937). It is a simple blood cyst attached to a vein and it appears clinically as a purplish tumor which expands with effort and is compressible It is of comparatively early onset but may be delayed until middle life It probably has a congenital basis in most instances but may be acquired. Varix of the neck is to be distinguished from cavernous hemangioma neurilipoma branchial cyst, emphysema and herniation of the *trachea*. Surgical excision may be rather challenging technically

See Guibal (RevChirParis 72 240, 1953) review; Jura (ArchItalChir 41: 101, 1935) 2 cases.

Angioma Serpiginosum is characterized by multiple telangiectases which may start from a congenital vascular nevus but which often arise spontaneously (Hutchinson ArchSurg 1 pt 9 1890) The primary lesion is a small, reddish angiomatous punctum Extension occurs by the appearance of satellite lesions, which coalesce to form large patches. The health of the patient is unaffected. The disease slowly extends, with a tendency to fade in the center Montgomery and Bailey (BJD 47 456 1935) reported a case and



Fig. 1468.—Angioma serpiginosum of thigh, in boy slowly spreading, papular in part hyperplastic and in part telangiectatic.

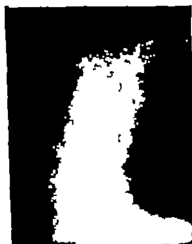




Fig. 1469—Anemic nevus of right nuchal region.

Fig. 1470.—Anemic nevus, section stained with orcein-polychrome blue blood vessels are absent elastic fibers are normal in amount. (Dr Stuart C. W y)

reviewed 57 others from English and American literature since 1913 This disease is to be distinguished from Schamberg s and Majocchi s, and from pigmented purpuric dermatitis of the legs. The case reported by Wigley BJD 58: 66 1946) was unusually widespread. Two cases were presented by Musso (BJD 65 25 1953) The few patients I have treated for this condition responded well to filtered x ray therapy in doses of 400 r at intervals of a month, like other hemangiomas.

Anemic Nevus is characterized by vitiligo-like areas, occurring singly or in groups, and differing from normal skin only in vascularity The lesions are generally rounded in shape, their borders being sharply outlined and irregular like the borders of the usual nuchal hemangioma. The surrounding skin is normal. The spots are made more apparent by friction, heat or cold, or light cupping Difference from vitiligo lies in the fact that there is no lack of melanin pigmentation. The lesion, white because of lack of blood vessels, is without textural change (Piorowski ADS 50 374 1944) It can occur as a linear systematized abnormality (Pace ADS 44 944, 1941)

Within the anemic nevus, the triple response of Lewis is defective, for the flare does not occur (Butterworth and Walters ADS 66 333 1959) The fault would seem to lie in the effector cells of the arterioles, for while the lesion is capable of sweating vasodilators do not redden it, and intradermally injected epinephrine does not increase its pallor nor do methacholine and pilocarpine elicit their usual pharmacologic responses.



Fig. 1471 —Hemangiopericytoma of the back. ([illegible] et al. ADS 58: 194, 1948.)

Blood Vessel Tumors may be divided into (1) benign hemangiomas, (2) hemangioendotheliomas which range from benign to malignant and are characterized by proliferation of endothelial cells, and (3) malignant endotheliomas (Pulford AnnSurg 82 710 1925) The name hemangioendothelioma was first used by Mallory (JExperM 10 575 1908) and defined by Stout (AnnSurg 118 445 1943) as a tumor featuring the formation of atypical endothelial cells in greater numbers than are required to line the vessels with a simple endothelial membrane and the formation of vascular tubes with a delicate framework of reticulin fibers and a marked tendency for their lumens to anastomose.

Hemangioendothelioma was reviewed by Caro and Stubenrauch (ADS 51 295 1945) in their report of an old man whose trouble began with discoloration of the scalp followed by swelling of the forehead eyelids and cheeks, and by late metastasis to the cervical lymph nodes. The disease began on the face spread widely and metastasized extensively in the case of Weidman (ADS 62 655 1950) and like a considerable proportion of similar cases was initiated, it seemed, by trauma An angiosarcoma of the leg an ulcerative

lesion, was reported by Holtzman and Grayzel (ADS 56 506 1947) Multiple malignant lesions were scattered widely over the body of an infant seen by Schwartz (ArchPediat 62 1, 1945) and proved rapidly fatal with widespread metastases.

Cultural characteristics of the cells of hemangioendothelioma obtained from a lesion of the calf of a young Negro were described by Murray and Stout (AmJPath 20 277 1944) they exhibited a membranous habit of growth which covered surfaces with a mosaic the cell borders cemented, and they differed from the cells of fibrosarcoma and leiomyoma.



Fig 1472.—Hemangiopericytoma, a nodule from case shown in Fig. 1471



Fig. 1473.—Hemangiopericytoma, higher magnification of tissue of Fig. 1472.

Malignant hemangioendothelioma developing in the scar and lymphedema resulting from radical mastectomy have been seen a number of times, forming a distinctive although rare picture (Stewart and Treves Canc 1 64 1948 Ferraro Canc 3 511 1950 Jessner et al.: ADS 65: 123 1952) The malignant process is accompanied by marked lymphedema and suggests clinically recurrence of the breast cancer The cases have occurred in women from 46 to 68 years of age who have had persistent postoperative elephantiasis. These tumors have all been radioresistant. Angiosarcomas of the hands and feet were discussed by Oughterson and Tennant (Surg 5 73 1939)

Metastasizing Hemangioma.—Robinson and Castleman (AnnSurg 104 453 1936) found 4 cases in the literature like the 1 they reported. Theirs began in the breast of a girl 18 years old. While it looked histologically benign, it was malignant Such tumors are radioresistant.

Endothelioma consists of proliferative lymph or blood vessel endothelium. Few authentic cases have occurred in the skin, according to Sweltzer and Winer (ADS 34 997 1936) who found only 6, 3 of which were suggestively associated with trauma. The lesions are of pea to orange size, dark red and fairly soft, and they may exhibit satellite nodules. They often ulcerate and *may bleed profusely but are not painful as a rule. The microscope* reveals the construction from capillary and capillary forming material. The lesions may be benign or of local malignancy. Malignant angioblastomas are with difficulty distinguished from reticulo-endothelial blastomas.

Hemangiopericytoma is the name applicable to vascular tumors with endothelial tubes and sprouts surrounded by closely packed, rounded and sometimes elongated cells which can be demonstrated by tissue culture to be derived from the capillary pericytes of Zimmermann (ZtschrAnat 68 29 1923). Lesions have been found in man in the kidney, heart, lung, intestine, pia mater and omentum, as well as in the skin. Recurrent or aggressively invasive cases comprised 21% of 110 reviewed by Kay and Warthen (Cancer 6 167 1953) and were located mostly on the leg or retroperitoneally. Congenital cases have not proved malignant (Cole et al. AD 72 328, 1955).

The skin was the site of origin in 8 cases reported by Stout and Murray (AnnSurg 116: 26 1942) and in 2 cases of Sims et al (ADS 58 194 1948). The thigh was the location in cases of Fisher et al. (AmJPath 28 653, 1952) and Kitamura and Takada (Hautarzt 4 56 1953). Pericytes are contractile cells of spider like shape with numerous slender dendritic processes which encircle the capillaries, demonstrable by silver-chrome impregnation technic. They are the origin of the enveloping mantle of the glomus tumor. The gross appearance does not enable distinction to be made *clinically from granuloma pyogenicum*, hemangioma, lymphangioma, angiosarcoma, glomus tumor or endothelioma, but the microscopic structure is diagnostic.

Treatment is wide excision and plastic repair or intensive x ray therapy.

ANGIOKERATOMA

Telangiectatic warts are characterized by telangiectases and the formation of hyperkeratotic nodules enclosing dilated capillaries. It was not until the publication of Mibelli (GiorItalD 1889 p 76) that an accurate delineation of the features of the malady was available. Matsumoto (UCutRev 1919 p 24) recognized several different types of angiokeratoma:

Mibelli's type, angiokeratoma Mibelli.
Atypical, symptomatic forms, angiokeratosum or kerato-angioma.
Hyperkeratosis in punctiform angioma, as of the scrotum.
Hyperkeratosis in senile angioma.
Angiokeratoma on the basis of congenital vascular nevus or tumor.
Angiokeratoma on the basis of postnatal telangiectasis.
Transitional forms, similar to changes occurring in varicose veins.

Angiokeratoma (Mibelli).—Mibelli's patient was a young girl, and the disease, which had been present for about 5 years, involved the dorsal aspects *of the fingers and toes. The lesions* ranged from hemp-seed to pinhead size. They were distributed along the superficial capillaries, which were slightly wider than usual. The patient had had chilblains for several years.

Histologically there were oval or irregularly rounded lacunar spaces in the rete, the majority of which possessed a regularly organized lining. Some spaces were partially or completely divided into compartments by thin septa, and most of them were filled with serum or coagulated blood. Chronic inflammatory changes were noted in the papillary and subpapillary layers, and an occasional distended tissue space was found partly filled with red blood cells. The papillae near the lesions were hypertrophied, and the interpapillary epidermis here and there extended deep in the dermis. The horny layer, greatly thickened, showed vesicles and medullary cavities. Normal sweat ducts were present.



Fig. 1474.—Angiokeratoma of a girl's thigh. (Dr Robert N Andrade.)





Fig. 1475.—Angiokeratoma, patellar region. (Dr Robert N. Andrade.)
Fig. 1476.—Angiokeratoma. (Dr Fred Weidman.)



Fig. 1477.—Angiokeratoma of scrotum.

Two cases were reported by Pringle (BJD 3: 237, 1891) His first was a woman, 4 years old, whose younger sister was similarly affected. The malady had been present 8 years. There was no swelling or hyperhidrosis of the extremities, but she had an ill balanced peripheral circulation as evidenced by rosacea, blushing, and frequent attacks of chilblains. The lesions were distributed over the dorsal skin of both the hands and feet. They ranged from pinpoint to split pea size. They were dark red in color and blood exuded when they were pricked. A second patient was also a woman 4 years old, and the malady which affected only the hands and feet, had first appeared 12 years previously. Pringle found thickening of the corneous layer and hypertrophy of the stratum lucidum. The granular layer was little changed. At the margin of the diseased area the rete Malpighii abruptly became greatly hypertrophied, the basement membrane remaining constantly present although broken in some places and ill-defined in others. The surrounding papillae were enlarged, and proliferative changes were noted in the tips of the elongated interpapillary plugs; but the papillae near the center of the lesion were flattened out, and the sweat ducts, in their course through this region, were malformed or even obliterated. The rete enclosed large irregularly oval spaces, as in Mibelli's case. Some of these were filled with blood coagulum. There were chronic inflammatory changes, consisting of copious leukocytic infiltration, marked fibrosis and general dilation of the blood vessels in the papillary and subpapillary layers.

In a man 39 years old reported by Anderson (BJD 10: 113, 1898) there was present, too, congenital deformity of the hands, a peculiarity which affected also his mother and sister, and 3 of 4 of the patient s children, similar to that seen in Dubreuilh's case The eruption was distributed over the trunk, limbs and genitals. The lesions, which ranged from pinpoint to hemp-seed size, were of the characteristic purplish red color and showed no tendency to coalesce. Judin (DZtschr 1905, p. 86) described a man 23 years old whose disease involved the first and second fingers of one hand and had bee present for 15 years. The lesions resembled those of angioma more than those of angiokeratoma. The patient of Zeisler (JCutGUDis 11: 490, 1893) presented typical lesions of angiokeratoma on the hands and feet, and many naevoid lesions on the legs, forearms and ears. Paul (BJD 30: 7 1918) reported an unusual case with many lesions on the face; there was a history of heredity through 4 generations. In the patient of Weber (BJD 30: 89 1918) hyperkeratosis was so marked as to give the lesion the appearance of a nevus unius lateris.

The disorder is commonest in individuals of chilblain circulation and the lesions are usually more pronounced during the colder months.

Angiokeratoma (Fordyce-Sutton).—A type of angiokeratoma distinct from Mibelli s as Wile and Belote (ADS 18 501 1928) noted, is that of Fordyce (JCutD 14 83 1896) and Sutton (J 57 189 1911) in whose cases the lesions were small, discrete asymptomatic reddish or purplish papules scattered over the scrotum In most of such patients seen by me (ADS 55 548 1947) the tongue showed beneath it and along its border the telangiectases which characterize Osler s disease a vascular anomaly of which I believe scrotal angiokeratoma to be one manifestation. In Fordyce s case the eruption was confined entirely to the region of the scrotum The patient was a man 60 years old, who had no vascular disturbance other than a double varicocele which had long been present.

Microscopically the lesions consisted of lacunar spaces, lined with a thin layer of endothelial tissue and filled with blood. These cavities occupied the papillary portion of the dermis, although some were enclosed within the rete Malpighii. At several points in the epidermis, which was but slightly thickened, tiny lacunae were found, but while these contained numerous blood corpuscles, their lining was unorganized and consisted only of disintegrated epithelial cells. Beneath the lower margin of the rete there was round cell infiltration, dilation of the capillaries, and deposition of blood pigment. In the 5 cases studied microscopically by Sutton, Sr., there was marked diminution of the elastic tissue in the affected areas. It is possible that the absence of these fibers hastens the vascular dilation the epidermal and corneous changes being, then, secondary

Angiokeratoma Corporis Diffusum.—Described by Fabry (AfDuS 43 187 1898) as nodular purpura hemorrhagica the disease is featured by a profuse eruption of small papules and macules with some hyperkeratosis, the lesions being dusky purple almost black. Ruiter et al (Dermatologica 94 1 1947) surveyed cases affecting 3 brothers and a fourth patient who died in uremia. These individuals had cardiovascular disease with renal abnormalities hypertension and dependent edema. Telangiectasis apparently affected pre-existing blood channels, particularly those of the dermis, where cavernous lesions filled with blood were found mainly in the papillary layer The same patients were reviewed by Pompen et al. (ActaMScand 128 234 1947) and by Ruiter (ADS 68 21 1953) Cases have been seen only in males, with onset

of symptoms before puberty Marked broadening of the media and swelling of the cells of the muscular layer of the vessels have been observed with similar changes in the muscle tissue of the heart. Stunted growth abnormalities of the spine, hypertrophy of the clavicles and contractures of joints were associated bodily defects in the young man described by Price (BJD 67 105 1955)

Etiology and Pathology.—The cause is unknown. Circulatory weakness, as evidenced by varicocele varicose veins or a tendency to the development of chilblains, constitutes a predisposing factor

Inasmuch as Mibelli s classification was purely an anatomic one, all cases satisfying the histologic requirements as he stated them, regardless of history or location, should be classed as angiokeratoma Though etiologically the scrotal type is different from the Mibelli Pringle type there is no means of further differentiating them than histologically and these studies are rather strikingly similar (Traub and Tolmach: ADS 24: 39 1931) Angiokeratoma bears out the opinion that circulatory weakness, such as exists in erythema pernio lupus pernio and dermatitis congelationis, is an important factor and the location of the lesions serves to indicate that external pressure plays a definite role (Way ADS 22 301 1930)

Liver disease is present in some cases. The change is probably primarily an injury of the blood vessel resulting in subepithelial and intraepithelial hemorrhage endothelial proliferation, fragmentation and loss of elastica, and perivascular inflammation (Wile and Belote ADS 18 501 1928) From verrucae vulgares the lesions are differentiated by the presence of dilated blood vessels.

Treatment.—High-frequency coagulation is effective. Solid carbon dioxide may be used (Cohen BJD 56 228 1944)

See Cottle (St George's Hosp Rpts 9 753, 1877 1878), first case I know of; Semear (JCutD 35, 542, 1917) woman' feet; Mirsch (PraktD 10 [illegible] 1935) 6 cases Jasnicka (ADS 34 [illegible], 1936) case affecting great toes; Taguchi (DWchn 107 1261, 1938), diffuse on body; Passano et al. (abs YBD 1940, p. 237) familial, Mibelli type; Sakon (ADS 51 155, 1945) case, involving face, arms, chest, thighs, legs Goldsmith and Hargreaves (BJD 58 [illegible], 1946) woman with systematized chest and leg lesions.

LYMPHANGIOMA

Neoplastic disease of lymph vessel tissue is sometimes only with difficulty distinguished from lymphangiectasis. Frequently the two processes are associated. Disorders of the lymphatics may be considered under the following headings

Lymphangiectasis.—Simple dilation, with or without vesicle formation may involve either the superficial or the deep lymphatics. Superficial lesions appear as several whitish or pinkish, pinhead to pea-size vesicles, which are discrete and usually grouped, and exude lymph profusely when punctured. They are soft and compressible but their coverings are tough and elastic. Lymphangiectasis involving deep vessels may be acute in onset but is usually chronic. It develops as a result of interference with the flow and may result in elephantiasis (q v) The overlying skin may look normal, the changes being appreciable only on palpation, or the skin may present numerous soft nodules, cystic growths, or irregular cordlike lesions.

Two cases secondary to tuberculous lymphatic obstruction were reported by Stokes (ADS 8: 495, 1923) In a case seen by White (JCutD 24: 501 1906) the belly wall was involved, but this was not discovered until after incidental laparotomy after which the discharge of straw-colored fluid from the incision was remarkably copious. Large patches of soft, yellowish tissue on 1 thigh of a woman described by Gottheil (JCutD 27: 277 1909) resembled xanthoma, but histologically proved to be lymphangioma tous. Elastic tissue was abnormal, and the case may have represented an elastic tissue nevus with lymphangiectasis.

Malignant angioendothelioma (p. 1123) has been known to arise in lymphangiectasis following radical amputation of the breast.

Lymphangioma Simplex is characterized by the occurrence of small, circumscribed compressible tumors composed of old and newly formed lymphatic vessels filled with fluid. The *lesions* are whitish or pinkish in color translu-





Fig. 1478.—Lymphangioma circumscriptum affecting left side of neck.
Fig. 1479.—Lymphangioma.



Fig. 1480.—Lymphangiectasis of thigh and [illegible] due to [illegible] of inguinal lymph nodes. (Dr. F. [illegible].)

cent and sparsely and irregularly grouped over the affected areas. The sites of predilection are the lips, mouth and genitalia. Elephantiasic edema and thickening of the underlying tissues may result. Lymphangiomas of this

type occasionally involve the tongue or lips, giving rise to macroglossia or macrocheilia. Pautrier (BSocfrançD 31 45 1924) reported a gigantic tumor involving the tongue. Histologically the lesions consist of enormously hypertrophied lymphatic vessels.

A lipomatoid mass with indistinct boundaries, 6 inches in diameter in the thigh of a man studied by Burman (AD 71 486, 1955) was productive during a 3-year period of intermittent drainage of clear watery fluid through the pores of the otherwise seemingly normal overlying skin to which it was attached. This singular example of the weeping of lymph through unbroken skin differed from the case of Oughterson and Tennant, quoted by Burman, wherein lymph flowed through an ulcerated, keloidal scar that followed incision of a subdermal lymphangioma of a boy's thigh.





Fig. 1461.—Lymphangioma. (Drs. John Fordyce and George M. MacKee.)

Fig. 1462.—Lymphangioma circumscriptum, showing intrapapillary lymphectasia. (Dr Fred Weidman.)

Lymphangioma Circumscriptum is characterized by a localized eruption of thick walled, pinhead to pea size opalescent, frog-spawn-like vesicles. The groups are generally few from 1 to 3 in number and the sites of predilection are the thighs, the upper arms and the mucous membrane of the mouth and tongue. The axillary and scapular regions also are frequently involved. The patches are of various sizes and shapes, but are generally 8 to 10 cm. in diameter. They may be single or multiple as in the case of Oliver (ADS 3 608 1921). The earlier lesions are small deeply seated, opalescent vesicles. Later as in the cases reported by White (JCutD 12 474, 1894) they may become thick rough and crusted, or even verrucose. When punctured however the character and quantity of the immediate exudate disclose their true nature.

Telangiectasia is a frequent accompaniment. Occasionally the affected area is the site of recurring erysipelatoid inflammation. The lesions develop early in life and are usually persistent They give rise to no subjective symptoms.

Pathology—The new formation of lymph vessels is primary dilation being secondary (Torok MonatshPrakD 14 169 1892) The vesicles, which are round or pear shaped cysts, are lined with endothelium and occasionally divided by septa They are situated for the most part superficially in the dermis. They are filled with granular matter lymph and fibrin, and sometimes contain leukocytes and even blood Pericystic round-cell infiltration may be found in accompaniment often with dilation and new growth of the capillaries The adjectives used in histologic description, simplex, hypertrophic and cavernous depend on the configuration of the neoplastic cell congeries. In the first, the vessels are small and uniform in caliber in the hypertrophic type the proliferated cells are massed together in the cavernous, dilation is the outstanding feature Combinations in a single specimen are common. Fich (MonatshPrakD 48 199 251 1909) clearly demonstrated that lymphangioma tuberosum multiplex is in fact syringoma being not lymphatic in origin.

Prognosis.—The lesions behave as benign tumors with rare exceptions.



Figs. 1483 and 1484—Cystic lymphangioma hygroma. (Gross and Goeringer SGO 69 48 1939)

Treatment.—Good results have followed the use of radiotherapy although the *lesions are fairly resistant.* They may be removed by excision or electric cauterization, but they often recur Gant (ADS 54 202, 1946) used solid CO_2 with a good result Treatment by means of the injection of sclerosing agents has been tried with success by Grund (ADS 36 947 1937) and Fonseca (abs J 112 582 1939)

See Francis (BJD 5 33, 65, 1893), review Elliott (JCutD 12: 137 1894) lymphangiectasia . . . eck Robinson (JCutD 13 476, 1895) 3 cases, 1 of which may be . . . Gilchrist (Bull JHH 7 . . ., trioma Bowen (Twentieth Century Practice 5 . . ., 1896) . . . 1896) Pollitzer (JCutD 24 494, 1906) 2 case Crocker (Diseases of the Skin, Blakiston, . . . p 9 . . .) mucosal . . . Simpson (J 66 949 1916), radium cure, Trimble (JCutD 37 . . . 1919) 3 cases, success with radium Brunauer (ArDuS 142 114 1923) . . . Hodges et al (AmJRoentg 42 881, 1939) Watson (JPediat 15 401 1939), . . . in children Vero (ADS 50 281 1944), sacral case; Eller and Eller (Tumors of the Skin, Lea & Febiger 1951 p 148) bibliography

Cystic Lymphangioma (Hygroma) is usually congenital in origin and commonly affects the anterior cervical region The lesions are thin-walled tumors containing lymph and lined with *endothelium* (Fleming J 110: 1699 1938) They are usually located in the lower part of the side of the neck and occasionally extend into the mediastinum If multilocular they are called lobulated capillary and cavernous types also occur in children. Rarely they are found in the axilla or groin They usually appear within the first 2 years of life but may develop at any time and they grow rapidly The treatment is complete surgical excision which may be technically a difficult undertaking (Compare venous varix

See Dowd (Ann Surg 58 112, 1913) 81 cases reviewed; . . . (AmJDisChild 41 . . . 1931) . . . after 1913 Gross and Goeringer (SGO 69 48 1939) 27 cases, half of them present at birth, 90% by age of 2 years

KELOID

Symptoms.—A keloid is a dense fibrous growth which develops in mesodermal tissue usually at the site of a scar and which is characteristically a smooth, firm, reddish scarlike tumor The keloids arising spontaneously and



Fig. 1485.—Keloid, following burn.





Fig. 1486.—Keloid from piercing lobe (Hall South M J 32 376, 1939.)
Fig. 1487.—Keloid at sites of acne lesions in Negro.





Fig. 1488.—Nuchal keloid, acne cheloidalis. (Dr Clyde Cummer.)
Fig. 1489.—Keloid, histologic structure. (Dr Fred Weidman.)

those resulting from cicatrix cannot be distinguished pathologically Keloids develop gradually the first appreciable lesion generally being a deeply seated, firm reddish dome-shaped nodule the surface of which is traversed by minute

tortuous capillaries. After attaining a certain size they may remain stationary or perhaps, rarely undergo partial or complete involution. Ulceration is exceptional but it does occur The lesions are often tender and are sometimes the source of spontaneous pain. When fully developed, the growths are oval, elongated or irregular in outline frequently with clawlike lateral projections They range from a millimeter to many centimeters in size and may consist of one globular mass or of a lobulated agglomerate. In number they vary from 1 or 2 to 100 or more





Fig. 1490.—Keloids over sternum, a common location.
Fig. 1491.—Astonishing case of keloids. (Drs. Moses Scholz nd J R. Kessler)

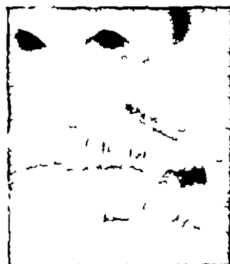




Fig 1492. Keloid f lip in Negro trumpeter (Drs. J ck W Jones and Herbert S. Alden.)
Fig. 1493 —Keloidal bundles of dense fibrous tissue deep in dermis (Dr Fred Weidman.)

The tip of the tongue of a trumpet player was the remarkable location of a keloid in the patient of Schmidt (DWehn 99 1341 1934) The lesions followed herpes zoster in the unusual case of Traub (ADS 52 203 1945) They have been known to follow vaccination (q v) although this is rare The only case in which malignant change has ever been recorded, a questionable one was that of Anderson (Lancet 1 1025 1888) The production of keloids in

ornamental designs has been practiced by some primitive peoples. Since the lesions may affect sexual selection, their predominance among Negroes may have a Darwinian explanation, hypothesized Bohrod (ADS 30 19 1937)



Fig. 1494.—Keloids and fibroma. (Drs. A. R. and W. L. Hollister.)



Fig. 1495.—Keloids of striking development and appearance. (Dr O. G. Costa.)



Fig. 1496.—Keloids following needle punctures in a drug addict. (Dr J. D. Shelmire.)

Etiology.—Predisposition is a strong etiologic factor There exists a familial tendency to the disorder Negroes are especially susceptible. An individual may develop keloid at the site of some injuries, while his tissue forms normal scars at other locations at other times. Analogies exist between keloid and xanthoma, and their common occurrence in acne, 12% according to Garb and Stone (AmJSurg 58 315 1942) suggests a hormonal relationship.

The growths are composed of extremely large homogeneous fibers, interspersed with a few connective tissue cells having small intensely staining nuclei. The skin glands and hair follicles are pushed aside. See Atomic energy injuries (p 115) and Treatment high frequency currents (p 96)

Prognosis.—The growths are persistent and spontaneous regression seldom occurs. They respond favorably to appropriate treatment however and improvement can fairly safely be promised.

Treatment.—Only x rays, radium and surgery are satisfactory. In attacking extensive growths x rays, 300 r each 3 weeks for perhaps 6 doses are effective. Radium is valuable in keloids of small size. Admirable results may be obtained from excision followed at once by an erythema dose of x ray therapy (Nason NEngJM 226 883 1942). Young soft fast-growing, small keloids respond especially favorably. Old large stationary hard growths are recalcitrant. Mere excision is generally followed by recurrence. Injections of hyaluronidase were combined with x ray therapy by Cornbleet (J 154 1161 1954), whose results were good. ACTH and cortisone were tried and found wanting by Ronchese and Kern (NEngJM 250 238 1954)

See Alibert (Maladies de la Peau, Paris, 1806, p 113) original description; Hutchinson (EdinMJ 43: 5, 1897) Heidingsfeld (J 53 1277 1909) Hertzler (Treatise on Tumors, Lippincott, 1912, p. 78); Smyth (BMJ 2 811 1913) injection of Formol; MacKee (J 66 1886, 1916); Pfahler (ADS 2 181, 1920) x ray and radium combined in treatment; Frieben (MünchMWchr 67 1343 1920) treatment; Kurtz (UCutRev 24 196 1920) radium; Albrecht (ADS 3 142, 648, 1921), pepsin digestion treatment; Taussig (CalifWM 21: 520, 1923) radium; Grier (AmJRoentg 16 32, 1926) x ray therapy; Pautrier and Woringer (AnnDerm 2 1145 1931) pathology; Siberstein (HandbHuG 12: 3 220 1932) histology; Wolf (WienMWchr 86, 722, 1936), familial; MacLeod and Cummings (BJD 48 245, 1936), following smallpox; Hintze (Strahlentherapie 57: 224, 1936) 25 cases, 6 of which were sternal, radiation therapy; MacKee (X rays and Radium in the Treatment of Diseases of the Skin, Lea & Febiger 1938, p. 663); Ashbury (UCutRev 42 441 1938), excise, give 500 r x-ray the next day; del Guidice (abs J 113: 1060, 1939), 300 cases treated by x ray; Costello (MedRev 154 295, 1941) treatment; Garb and Stone (AmJSurg 58 315, 1942) 86 cases; Hunter (Radiol 39: 400, 1942) 931 cases, 200 x ray at 130 KVP 3 mm. Al., each 2 weeks; Costa (ADS 48 421 1943), amazing case, neck; Marshall and Rosenthal (AmJSurg 62 348 1943), etiology; Cutter (ADS 50 308, 1944), Gorri's description in 1830; Marshall (NOrlMSJ 97 15, 1944), cause and cure; Traub (ADS 49 278, 1944) following chicken pox; Strand (ActaRadiol 26 397, 1945) radium mold; Bloom (ADS 55 426, 1947) occurrence in Negro twins; Fisher and Keefer (AmJRoentg 59: 378, 1948) radiation therapy; Warren (JMoMA 45 344, 1948), following tonsillectomy; Lindsay (ADS 58 583, 1948) Cadalso treatment with sodium fluoride, 20 mg. orally daily; Marshall and Schaleberg (WiscMJ 49 300 1950) serum of keloid rich in globulin and attracts fibroblasts, reversed by injections of hutaprene [illegible]; Edmundson (ADS 64: 271 1951) following chrome ulcer unique; Robertson (LdnMJ 56: [illegible] 1951) at sites of epinephrine injections; Braun-Falco and Weber (DWchr 174 796, 1951) [illegible] hyaluronidase, 25 units per 0.5 to 1.0 cc injected daily or on alternate days, painful and vigorous reactions; Findlay and Stoughton (AD 71 599 1955) 3 typical cases with hyperplastic collagen bundles and unusual interstitial material.

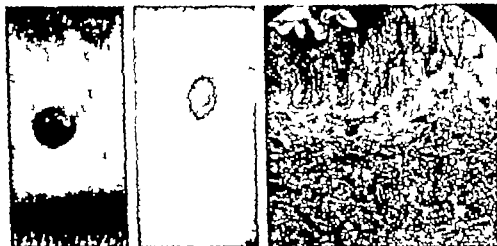
NODULAR SUBEPIDERMAL FIBROSIS

Also known as hard fibromas, dermatofibromas, histiocytomas and noduli cutanei, these lesions are firm, reddish yellow nodules set in the dermis, the smooth surface usually rising slightly above the general level, sometimes being depressed somewhat below it. They begin as small infiltrations which enlarge fairly rapidly to a diameter as great as 1 cm., sometimes larger. They are hard sharply defined little tumors which may occur on the trunk or extremities of either sex at any age (Michelson ADS 27 812 1933; Senear and Caro ADS 33 209 1936). When one compresses the lesion between the fingers the margin of induration is found to extend a millimeter or more beyond the visible edge, and the skin wrinkles over this intracutaneous border. It is common to observe that one or several make their appearance during pregnancy. While a nodule tends to remain stationary for years after having reached its full development it may sometimes slowly involute to leave a soft scar.

A large solitary lesion overlying the patella in the case of Lewis and Sachs (AnnIntM 9 1746 1936) simulated a sarcoma but proved histologically to be a lipoidal histiocytoma and it was successfully excised. Multiple lesions were the sequel to insect bites on the extremities in the case of Carleton (BJD 60 378 1948). Multiple lesions of the face were seen by Cathcart

(ADS 61 334 1950) I have removed 1 from the palm and another from the oral mucosa quite unusual locations. A scrotal lesion was seen by Ketschmer (J 132 143 1946)

The lesions are probably not neoplastic in the blastoma sense but consist of adventitial cells, sometimes laden with lipid, occurring with suggestive frequency in persons whose families contain diabetic sibs (Arnold and Tilden ADS 47 408 1943) The demonstration of fat within the cells of the tumors, indicating that they are composed of phagocytic histiocytes was first made by Pautrier and Woringer (BsocfrançD 40 1658 1933) Intracellular lipids were found in 15 of 25 lesions by Senear and Caro (ADS 33 209 1936) In some of these iron was also present presumably of blood origin (see hemosiderinotic histiocytoma) Pathologically they range from small, scarlike fibrous nodules with few capillaries no pigment no lipid and no histiocytes, to highly vascular lesions with numerous phagocytes filled with hemosiderin and lipid, stated Stout (JMoMA 44 595 1947) who called them fibrous xanthomas and disagreed with Gross and Wolbach (AmJPath 19 533 1943) who thought them sclerosing hemangiomas, as did Dawson (EdinMJ 55 655 1948) The stage or degree of sclerosing involution Dawson attributed to the range of histologic picture from a cellular angiomatous structure to an almost pure fibromatoid or xanthomatoid tumor



Figs. 1497 1499.—Nodular subepidermal fibrosis.

Fig 1497 A lesion of forearm. Fig 1498 A lesion from scapular area Fig 1499 Histologic structure, showing interlaced bundles of cells in fibrotic tissue beneath the papillary layer of the dermis.

Reviewing 101 lesions obtained from 95 patients, Rentiers and Montgomery (ADS 59 568 1949) found that one third of them contained histiocytic phagocytes and the others were entirely fibroblastic. Their patients did not show increase in plasma lipid but the tissue lipids were elevated in the histiocytoma group. They lacked the systemic manifestations of xanthoma and among them there was no increased incidence of diabetes, hypertension or other recognizable metabolic disorder

Hemosiderinotic Pigmented Histiocytoma (Pseudomelanoma).—Histiocytoma may follow a minute, hemorrhagic injury and the fixation of the blood pigment within it results in purplish brown pigmentation of the tumor which clinically bears close resemblance to malignant melanoma. In the cells, the *Prussian blue microchemical test* shows the pigment granules to be iron-containing melanin is iron free (Bernstein ADS 40 790 1939) Blue nevus and melanoma are to be distinguished.

Treatment.—The lesions are benign and do not need to be removed. If they are excised the margin must be generous in order to prevent recurrence

in the scar The pigmented lesions offer diagnostic difficulty but an experienced dermatologist is not likely to diagnose melanoma and subject the patient to radical surgery X ray therapy may be used doses of 800 r at 120 KV with 1 mm. Al. may be given at intervals of 2 months for 3 or 4 treatments, and may be expected to flatten and soften the lesions considerably

HISTIOCYTOMA.—Arning and Lewandowski (AfDuS 110 5, 1911) Schreus (AfDuS 161 456, 1930), Traub and Monash (ADS 26 250 1932) preferred the name "dermatofibroma" Stecker and Robinson (ADS 43 498, 1941) dermatofibroma, pathology and review Teruins (AnndeD 78 409 1951) cutaneous fibromas, diabetes and obesity

HEMOSIDEROTIC HISTIOCYTOMA.—Montpellier et al. (BsocfrancD 46: 728, 1939), histiocytome noir 3 cm., solitary lesion, man's thigh Dobkevitch and Marques (BsocfrancD 46 1188, 1939) 2 cases with repeated hemorrhages within the lesions Foot (AmJCancer [illegible], 1939) neurofibrils in melanotic xanthomas Sutton and Sutton (Introduction to Dermatology Mosby 1941, p. 364); Weidman (ADS 51 108, 1945) hemosiderin in [illegible] xanthoma [illegible] and Powell (BritJSurg 38: 442, 1951)



Fig 1509.—Painful nodule of the helix.

CHONDRODERMATITIS NODULARIS CHRONICA HELICIS (PAINFUL NODULE OF THE EAR)

Symptoms.—Winkler (AfDuS 121 278 1916) under this title described a small, nodular painful growth occurring on the rim of the ear Foerster (JCutD 36 164, 1918) independently reported 4 typical cases.

The growth is a solitary ovoid well-defined, firm sometimes warty nodule a few mm. in its longer diameter embedded in the skin, usually being movable over the underlying cartilage The nodule is flat topped, or slightly convex, with a sloping margin, and has a shallow depression filled with an adherent scale After reaching a certain size it ceases to enlarge and remains unchanged for periods of years. There is no malignancy

The usual location is on the superior aspect of the helix at or close to the site of Darwin's tubercle It may be on the anthelix, where skin is tight over the cartilage and is compressed when one lies on his side

The pain to which this tiny tumor gives rise is surprising When the patient rolls over during sleep it wakes him. He is never reluctant to allow excision, even though visible deformity trivial as this may be ensues. He is willing to undergo excision several times if the lesion proves to be recurrent which is by no means uncommon

The growths appear suddenly without history of previous injury and having appeared they remain indefinitely Males are preferred 10 to 1 reported Hand (ADS 61 862 1950) Culver (CalifWM 31 414 1929) reported more than 20 cases occurring on the Pacific Coast Poth (TexasSJM 33 19, 1937) found 73 cases reported only 7 of which involved women. Pirila

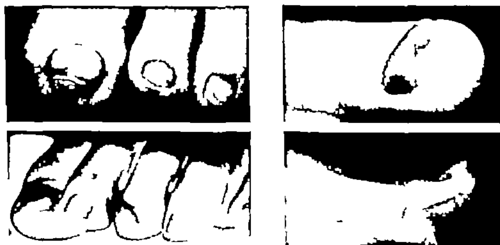
and Boulle (ParisMéd 1 60 1936) reported 12 cases under the title angiokeratoma. The disorder is fairly common, yet some otologists are not familiar with it.

Pathology.—Foerster (ADS 11: 147, 1925) found a diffuse inflammatory and degenerative process of the dermis, with epithelial hypertrophy. Woringer and Zoon (BeocfrancD 1938, p. 668) reported the occurrence of abundant nerve fibers in the tissues of 6 cases. A vascularized, organizing inflammatory lesion is found histologically extending to the cartilage which is affected only secondarily according to Newcomer et al. The structure in 23 cases was examined by Ebenius (ActaRadiol 22: 563, 1941) who thought the lesions might be precancerous. He recognized that in order to cure, excision must sacrifice a bit of cartilage as well as the affected skin a view shared by Bellesario (BJD 61: 296 1949).

The histologic study of Shuman and Helwig (AmJClinPath 24: 126, 1954) utilized 100 male cases from Army material. Characteristic features were (1) nodular epidermal hyperplasia, centrally ulcerated or depressed, and capped by a hyperkeratotic or parakeratotic scale; (2) edema, homogenization and fibrinoid degeneration of collagen, with or without crust formation; (3) proliferation of a richly vascularized granulation tissue associated with the cellular infiltrate of chronic inflammation; and (4) perichondritis, with or without degeneration of the elastic cartilage.

Treatment.—The usual procedure is excision, but recurrence is not unusual. Radiation therapy is unsuccessful. The application of bacitracin ointment was alleged to have cured 8 of 9 cases so treated by Nelson (ADS 65 356 1952). Recurrence after surgery took place in 18 of 58 cases of Newcomer et al. (ADS 68 241 1953), so they tried procaine infiltrations of the lesions. When this was done daily for 7 days in 9 patients 5 seemed cured, 2 were not helped, and 2 relapsed.

See Mitchell (ADS 7: 131, 1923); Roxburgh (BJD 39: 113, 1927), cause unknown; Dubreuilh and Pigeard (AnnDeD 6: 721, 1928) 6 cases; Meirowsky (DWchn 88: 243, 1929) histology; Fox (ADS 19: 1016, 1929) case, bilateral antihelical, due (?) to pressure; Klauder (ADS 21: 831, 1930) 3 lesions, not painful, on the ear of a woman; Halter (DZtschr 73: 270 1936) complex etiology includes perhaps peculiarity of blood vessels.



Figs. 1501 1504.—Subungual exostosis. Fig. 1501 (upper left) shows classic lesion of great toe. Fig. 1502 (lower left) is of middle toe, a less common location. Figs. 1503 and 1504 (on the right) show a great toe lesion and its roentgenograph, a patient of Dr Sam E. Sweitzer.

SUBUNGUAL EXOSTOSIS

A small, solitary nodular benign bony anomaly is occasionally seen, developing generally from the medial aspect of the terminal phalanx of the great toe in young adults. The lesion, a smooth bulging one as a rule, gives symptoms because it is pressed by the confinement of the shoe. A corn may develop on its glazed, firm surface. X ray examination reveals a pedunculated, rounded, mushroom-shaped nodule of bone attached to the phalanx. This variety of osteoma is covered with a layer of cartilage and enlarges by a process like ordinary ossification in cartilage according to Muir (Text Book of Pathol

ogy Wood, 1936 p 219) After reaching a maximum size in a year or two, it stops growing Clinically it may be mistaken for ingrowing nail, verruca, fibroma or malignancy In rare instances the lesions are bilateral.

Treatment is surgical After securing local anesthesia of the toe a rubber band is applied to the digit proximally to secure hemostasis. The nail is got out of the way sufficiently with blunt dissection and nail nipper and the configuration of the bony tumor is clarified by probing with the point of the tool which is then used to bite off the tumor at its base. I apply the cautery to the phalanx and dress the wound which proves to be painless, with, for example tetracycline ointment. The nail regrows without deformity The lesions treated as described do not recur

See Hutchinson (Lancet 2: 246, 1857) case, De Mson (AmJOrthopSurg 14 184, 1916), 5 cases Kurtz (BGO 43 480, 1926) 42 cases Shaffer (ADS 24: 371, 1931) review bibliography

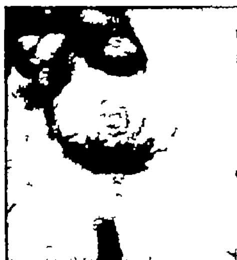




Fig. 1505.—Osteomas, congenital (Vero et al.: J 129 728, 1945.)
Fig. 1506.—Osteoma, histology (Vero et al: J 129: 728, 1945)

OSTEOMA OF THE SKIN

True bony deposits in the skin are exceedingly rare. Their nature is seldom recognized until the tissue has been examined microscopically The lesions may be single or multiple. They are round sharply defined, and hard Ossification in the skin may take at least 6 forms, according to Sehrt (AfPath Anat 200 395 1910)

True osteoma in the skin
Ossification in calcified dermoid cysts
Ossification and calcification in retention cysts
Ossification in other tumors of the skin
Bone formation in chronic inflammatory lesions
Stones in the subcutaneous adipose tissue solitary or multiple freely movable generally located in the extensor aspects of the legs of old people influencing the skin secondarily by extension.

Metastasis to the scalp from an osteosarcoma of the humerus was observed by Finnerud (ADS 10 56 1924)

Ossification may develop in surgical as well as other scars (see Pusey Principles and Practice of Dermatology Appleton 1926 p. 1094 Beintema ActaD-V 19 49 1938 Lilga and Burns ADS 46: 872, 1942)

The ossification of milia forming small flat whitish or pinkish tumors scattered over the face and neck, was long ago observed by Hopkins (ADS 18 706 1928) and similar lesions have been reported by Costello (ADS 56

536 1947) Leider (ADS 58 168 1948 61 329 1950 62 405 1950) Carney and Radcliffe (ADS 64 483 1951) and Gasner (ADS 69: 101 1954) Shotty papules in a woman's face probably represented ossification of milia, reported by Cannon (ADS 53 208 1946)

Calcification of congenital sebocystomatosis is a plausible interpretation of the case affecting a baby boy with lesions on the side of the scrotum and left thigh and adjacent skin. A comparable nevoid lesion widespread with hard, firm lumps affecting scattered areas of the body was seen by Scott and Temple (AmJDisChild 77 758 1949) There were multiple tumors containing bone in the case of Artz (ArDuS 151 396 1926)

Calcification in a pigmented nevus of the chin was reported by Heidingsfeld (AfDuS 92 337 1908) Heterotopic bone was present in a pigmented nevus of the cheek of a woman, present since childhood, described by Meltzer (ADS 62 696 1950) The patient of Becker (ADS 10 163 1924) had a scalp lesion, curiously cicatricial and chronic, from which bits of bone discharged. A congenital scalp lesion with osteosis was reported by Combes and Vanina (ADS 69 613, 1954) A congenital abnormality, probably an abortive supernumerary digit constituted the osseous lesion of the skin of the hand in the case of Dietrich (ADS 41 562, 1940)

See Musger (ActaD-V 16: 1, 1935) basis of bone formation is always pathologically altered tissue in tumors, inflammatory lesions, arkosity circulatory disturbances; de Gasantha (AmJClinPath 7, 10, 1937) rapid decalcification technic Wilson (AnnSurg 113 95, 1941) extraskeletal ossifying tumors perhaps derived from neuro-ectodermal cells; Stow II and Cramer (ADS 46 274, 1942) osteosis in degenerating epithelial islands in anaplastic methylcholanthrene mouse tumors; Tidens and Rutter (ActaD-V 29 140, 1949) extensive osseous tumor formation in defective female infant, who developed Lawrence-Moon-Biedl syndrome

See also Milium, calcification in; Calcinosis cutis Calcifying epithelioma.

LIPOMA

Dermal or subcutaneous new growths are seen composed of fat cells enclosed within a capsule of connective tissue. They are spheroidal or lobulated and exhibit great range in size. The growths consist of irregularly large adipose lobules, thinly encapsulated in fibrous envelopes, the septa of which carry the nutrient vessels but lipomas may be infiltrative in character with fine tongues of fatty tissue projecting outward along the blood vessels and between the muscle bundles. Increase in size is usually gradual. The tumors are freely movable They seldom give rise to symptoms. They are almost always benign but liposarcoma (q v) is known. They generally make their appearance at middle age and occur in order of frequency in the regions of the shoulder back neck, arm forearm axilla and thigh (Hogue WestJSOG 50 332 1942) The temperature of the skin over lipomas is lower than elsewhere a fact of possible diagnostic aid (Burrows Lancet 2 1198 1923) A pedunculated, ulcerating lipoma of 14 years duration in which the tumor was as large as the patient's head, was recorded by Hadley (J 101 1397 1933)

Familial occurrence which is not unusual was noted by Miller (J 106 2059 1936) a mother daughter and son being involved. In the family described by Humphrey and Kingsley (ADS 37 30 1938) 6 tumors were found in 18 sibs. Lipomatosis was inherited as a simple dominant in the family studied by Muller (Dermatologica 103: 258 1951)

Lipomas of the conjunctivae occurred in 3 generations (Saebø Acta Ophth 26 447 1948)

Lipomas of the tongue were classified by Spencer and Cade (Diseases of the Tongue London 1931) as (1) solitary and superficial, often pedunculated (2) intermuscular and deep (3) multiple and (4) diffuse, the rarest type A huge lipoma of the tongue was observed by Smith (J 108 522, 1937) and another by Paul (Lancet 2 997 1938) Somewhat smaller a soft, rubbery smooth but lobate superficially located lesion of the tongue was reported by Braunstein (J 140 165 1949) Latteri (Napl 7 266 1928) reported an interesting case in which the floor of the mouth was involved.

In the epigastric region small hernias often strongly resemble lipomas. Lipoma like lesions may develop at the sites of injections of insulin (see dermatitis medicamentosa). Weber (MP&Circ 209 203 1943) provided an interesting review of lipomatoid dysplasias of the subcutaneous tissues. See also Fat necrosis (p 198) and Panniculitis (p. 1014).

Painful Sacroiliac Lipoma.—Painful spots over the sacroiliac joints due to inconspicuous lipomas were noted by Ries (AmJObGyn 34 490 1937). These are not rare he said, and are located within 5 cm. from the sacral dimples; they are oval measuring about 2 by 3 cm., and are tender on manipulation. They may be successfully excised or injected with 2% Novocain.





Fig. 1401.—Lipoma, unusually large.

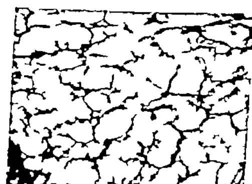


Fig 1409.—Lipoma, histologic structure.

Fig. 1407.—Lipomas of forearm. (Dr Sam E. Sweitzer.)

Lipoma Telangiectaticum.—In rare lesions, the structure may be so vascular as to justify this name although these are probably actually hemangiomas (q v). Lipomatous, unilateral, systematized nevi are on record (Robinson and Ellis ADS 35 485 1937).

Treatment.—Enucleation is the only successful plan, care being taken to remove all of the fatty tissue and its capsule. Generally lipomas may be neglected. If sarcoma is suspected excision must be wide.

Liposarcoma is divided by Stout (JMoMA 44 586 194) into 3 groups. The first is myxoid and limy on gross section with areas of embryonal yellow fat if the tumor remains well differentiated. It does not metastasize but it frequently recurs if incompletely removed. The second shows rounded cells without nuclei, some cells being of spindle shape as in fibrosarcoma. The tissue resembles embryonic brown fat and the lesion is malignant. The third type consists of tumors combining the elements of the first two and is fully malignant. Liposarcoma is the second most common soft sarcoma. Sixty per cent of Stout patients have been past 40. Sometimes the lesions are huge; one on record weighed 275 pounds. The lower extremities buttock and retroperitoneal tissues are the sites of predilection and the patients are generally of mature age. The growth is slow but recurrences are of seemingly higher malignancy (Ackerman and Wheeler: SouthMJ 35 156, 1942). The tendency to recur is noteworthy and they sometimes metastasize. Nine cases were reported by Moreland and McNamara (Surg

164, 1942) and 41 were accumulated by Stout (AnnSurg 119: 86, 1944) An interesting case was presented, along with a review of the subject, by Koritschoner (CentralblAllg Path 33: 145, 1923) The name hibernoma is used by some authors to distinguish tumors containing brown fatty tissue. Some of these are malignant.

Treament must be radical, and surgery is the only curative means, amputation being sometimes unavoidable.



Fig. 1016.—Diffuse lipomatosis. (Dr Grover W Wende.)

ENDOMETRIOMA
(ENDOMETRIAL HETEROTOPIA MENSTRUATING TUMOR)

Endometrioma is a tumor composed of dense fibrous tissue smooth muscle and adenoid structures. Cysts in such lesions, lined with cylindric epithelium are filled with material of chocolate color derived from blood. The occurrence of a neoplasm located at the umbilicus in a woman 35 to 55 years of age and its swelling pain and, perhaps, bleeding at menstrual periods are unique features. The lesions can result from implantation of endometrial tissue in laparotomy scars (Kaufman and Wilensky: Surg 4: 708 1938)

In the skin endometrioma is a rare tumor but most of the cases which are seen appear at the umbilicus (Cullen The Umbilicus and Its Diseases, Saunders, 1916 p 373) about the vulva (Jeffcoate BMJ 2: 1219 1936) or in the inguinal region (Moloney: BMJ 1 435 1949) A skin lesion continues to menstruate even if the uterus is removed, provided ovulation occurs.

Treatment is excision. The lesions are benign.

CULLEN'S SIGN.—A purpuric stain appearing at the umbilicus is so designated. It signifies subperitoneal hemorrhage generally the result of ectopic pregnancy

THE UMBILICUS is a region subject to various dermatologic abnormalities, including cysts originating from urachus or allantois, allantoic polypi dermoid cysts, and concretions as well as angioma verruca granuloma pyogenicum and other skin tumors. See Cullen (The Umbilicus Saunders, 1916) Gerard (Clin J 67 162 1938) A solitary red moist polyp resembling granuloma pyogenicum in an infant s navel proved to consist of ectopic gastrointestinal mucosa reported Shaffer et al. (ADS 70 217 1954) Red cellulitis appearing about the umbilicus in the presence of the surgical abdomen is likely to signify Meckel s diverticulitis (DeNicola J 154 1083 1954) Carcinoma metastasizing to the umbilicus was exemplified by 5 cases reported by Schiebel et al. (J 157 1489 1955)

See Cullen (SGO 35 257 1922); Edwards and Spencer (ArchSurg 11 634 1925), umbilical, J cobsen (AmJObGyn 6 257 1923 Arch Path 1: 169 1926; 5 1934, 1927) auto-transplanation experiments, etiology review Weller (AmJPath 3 553, 1927) 2 umbilical cases, muscle tissue absent Nielsen (ActaObGyn 14: 322, 1934) 17 external cases of endometrial heterotopia Cornweller (AmJObGyn 36: 8 7 1938) internal endometriosis Bego (ArchSurg 37 642, 1938) 87 umbilical cases Tausch (ArGynak 168 8 1939) cases, various locations.



Fig 1511 —Endometrioma, howing endometrial tissue beneath acanthotic epidermis, as umbilical lesion (Dr Bernard H. Winston.)

LEIOMYOMA

Tumors composed of smooth muscle fibers occur occasionally in the skin and subcutaneous tissues. They may be solitary or multiple and, when multiple they may be grouped or unilaterally systematized.

Solitary tumors were well described by Stout (AmJCanc 24 255 1937) who commented that glomus tumors (q v) are not the only subcutaneous painful ones. Stout found over 80 cases reported and studied 15 of his own. There was no predilection as to sex age or race The locations of preference were the extensor surfaces of the extremities the nipple regions and areolae scrotum labia majora, and sides of the face these being the places where smooth muscle is found normally in the skin

The lesions are small, being as a rule 2 to 15 mm. in diameter but they may grow larger even to the 9 by 6 cm dimensions of Stout s largest They are round and nodular usually elevating the superjacent skin but rarely they are pedunculated They lack distinctive coloration, but if shallow may be of brown reddish or bluish hue They are encapsulated and freely movable In 12 of 15 cases there occurred nonradiating pain in paroxysms, which might be spontaneous or provoked by cold fatigue trauma or pressure The pain was of momentary duration in some and lasting or waxing and waning in others it was described as stabbing pinching burning or griping in character Injection of epinephrine increase the pain In one patient the tumor doubled in size during pregnancy

Superficial growths in some instances are grouped in irregular patches, the number of tumors in each collection ranging from 2 or 3 to 100 or more

and the lesions bearing considerable resemblance to fibromas (Sutton J 59 178 1912) In cases presenting more than a single group of lesions, the arrangement is asymmetrical and the distribution may be as in a nevus unius lateris.

The more deeply situated tumors are usually solitary and round or oval in shape and the overlying skin is apparently normal The color of the affected areas ranges from chamois to dark red. The tumors are of firm con





Fig 1512—Leiomyoma of the skin, typical example. Photomicrograph from the case is shown in Fig 1513. (Dr Kendall Frost)

Fig. 1513—Leiomyma, showing character and arrangement of muscle fibers in lesions of Fig 1512. (Dr Kendall Frost.)



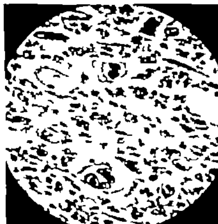


Fig. 1514—Leiomyoma of left clavicular region (Dr Clyde L. Cummer)

Fig. 1515.—Rhabdomyoma, nodule from skin of woman breast (Dr Stuart W y)

sistency and exhibit no tendency to ulcerate or metastasize They develop slowly are always benign and never become adherent to subcutaneous structures. The peculiar paroxysmal pains, which are present in a large proportion of the cases, seldom develop before the growths attain the size of a pea

The average age of the patients reviewed by Sutton (1912) was 34.5 years. The sexes were equally affected. In 65% of the cases the limbs were involved in 40% the face and in 30% the trunk. More than half of the patients suf

fered from paroxysmal attacks of pain in the affected region, while in 15% of the cases the tumors were painful only on pressure. Fifty per cent of the growths seemed to have originated in the arrector pili muscles, and 16% in the muscular coats of the blood vessels. In only one instance did any tumor disappear spontaneously. Superficial ones generally caused little discomfort but deep ones were painful. Ormsby (ADS 11 466 1925) emphasized the painful character of the lesions, particularly in cold weather pain and sensitiveness having been present in 70% of his cases.

Etiology and Pathology—The cause of myoma is unknown. The tumors consist of smooth, spindle-shaped, nucleated muscle fibers, aggregated into narrow bundles, running in various directions, and embedded in a more or less abundant stroma of connective tissue. The muscle cells contain the characteristic rod-shaped nuclei with rounded extremities, set in a matrix of finely fibrillated protoplasm, with no distinct line of demarcation between the cells (Heidingsfeld: J 42: 563, 1907)

Of the classifications which have been proposed, that of Babès (Ziemssen's Handbook of Diseases of the Skin Wood, 1885 p. 606) is as good as any:

(1) Myomas springing from the vessel wall by proliferation of the muscular elements, ' angiomyoma cutis. These growths are usually circumscribed, solitary and deeply seated. In relation to the nerves they sometimes form irritable tumors, ganglion dolorosum myomatosum. [These are now described as glomus tumors, q v]
(2) Hyperplasias of the arrectores pilorum:
 (a) As portions of vascular nevi (Virchow)
 (b) Forming multiple tumors.
(3) Neoplasms derived from the deep muscular layers of the skin, myoma dartique of Besnier :
 (a) Diffuse as in forms of elephantiasis lymphangiectoides and pachydermia myxomatodes.
 (b) Circumscribed. These may be polypoid, telangiectatic, or multiple, and the last are painful.

Histologically Stout found 2 types, those with and those without association with blood vessels. In vascular lesions, the walls were thick, the lumina were usually small and empty and the tumor parenchyma was continuous with the smooth musculature of the vessels. This type is generally deep and well encapsulated. Avascular ones, circumscribed but not well encapsulated, probably derive from skin musculature. Cajal staining reveals delicate neurites possibly connected to the smooth muscle fibers but not sensory (Stout: AmJCanc 29 435 1937)

The specific staining of smooth muscle fibers is somewhat disappointing. Pinkus told me (*pers. comm.,* 1935): *Theoretically every* good trichrome stain, such as the old Van Gieson mixture, or the more modern and contrasty trichrome stains of Masson and their modifications, should differentiate smooth muscle fibers from connective tissue fibers. In normal tissues, Van Gieson s stains muscle yellow like all cytoplasm, and collagen, red. Masson s mixtures stain muscle red and collagen green or bl e. However in leiomyomas there is often so much fibrous stroma and reticulin fibers that stain like collagen, that I cannot be sure, always, whether I am dealing with a leiomyoma with much fibrosis, or a fibroma with numerous cells, for the cytoplasm of fibroblasts stains the same as the cytoplasm of muscle cells. Mallory s phosphotungstic acid hematoxylin stains the cytoplasm of smooth muscle cells rather specifically

While malignancy may supervene it is very rare. A malignant case originating on the ankle, twice recurrent and metastasizing to the inguinal nodes, was reported by Gaté et al. (BSocfrançD Réun. Strasb., 1939 p. 931)

Diagnosis.—The lesions may be confused with those of fibroma neurofibroma nevus, histiocytoma, glomus tumor lymphangioma syringocystadenoma or even xanthoma tuberosum. Microscopic examination is requisite for positive identification.

Treatment.—Leiomyoma is not radiosensitive It is benign, and curable by excision. It may be neglected if not painful.

See Crocker (BJD 9 1 47, 1897) case, grouped on chin, review Herzog (JCutD 16: 527, 1898) grouped on cheek Whit (JCutD 17: 260, 1899) grouped on cheek Sarasin (BJD 32 229, 1920), Brook case follow-up Scholtz (ADS 10 172, 1924) multiple on left arm, Frost (J 83 966 1924) illustrations Hagens (DWchr 80 472, 1925) etiology Kerykas (DWchr 99 1110 1934), systematized, lumbosacral Stout (AmJCanc 31: 31, 1937) (recurr; Müller (ADS 43 875, 1941) grouped on back and chest Hadermacker and an [illegible] (Dermatologica 83 201, 1941, multiple, painful, systematized on trunk Arday (ADS 46: 114, 1942) xtensiv dissemination Lady (ADS 49: 202, 1944) spontaneous disappearance of some lesions Finnerud ADS 54 744, 1946) extensiv e distribution; New (ADS 60 [illegible] 1949) multiple systematized, thoracic Roeck (Proc. Twelfth Meeting Northern Dermat. Soc. 1949 p. 218) same nu mber f disseminated lesions; Cipollaro (ADS 60: 350, 1949), [illegible] systematization, bilateral Leavell (ADS 61: 188, 1950) zosteriform, onset at age 21; Christopherson (ArchSurg 60 779, 1950) 5 solitary lesions; Jansen (ActaD-V 32: [illegible] 1952), 13 cases 4 from subcutis vessel walls, 6 from rrectores, 1 dartoic in female, 2 multiple systematized.

GRANULAR CELL MYOBLASTOMA

This is a lesion *rarely encountered in dermatology* It *occurs in the* tongue (Klemperer AmJCanc 20 324, 1934) as a comparatively benign, firm, slow-growing tumor surmounted by proliferating epithelium so as to resemble a carcinoma, well delimited but seldom truly encapsulated, and identifiable histologically by the ribbonlike syncytial masses and large polygonal, myoma cells with granular cytoplasm but without striations. Mitoses are rare. Howe and Warren (Surg 16 319 1944) collected 168 cases, 56% of which were located in the upper respiratory and digestive tracts, 59 involving the tongue, 3 of which were malignant.



Figs 1516 and 1517—Cutaneous myoblastoma, the skin tumor and photomicrograph of its structure. (Lewis and Scott: ADS 44 84, 1942.)

Cutaneous myoblastomas are usually solitary asymptomatic lesions ranging in diameter from a few mm. to several cm., sessile or pedunculated, slow to enlarge eventually ulcerating affecting individuals of from 30 to 60 years of age as a rule. They may appear at any age however and 3 cases involving children were reported by Cave et al. (AD 71: 579 1955) whose essay was a comprehensive one Several cases of multiple tumors are on record, Cave et al *noted, and, while the tongue has been the site in about one third* and the skin in one fifth myoblastoma has been known to occur in the external auditory meatus (Horn and Stout SGO 76 316 1943) bronchi, common bile duct (Coggins ArchPath 54 398, 1952) maxilla parotid gland, larynx, breast, orbit heart esophagus, bladder urethra, perineum, anal region and ovary

The cells are large irregular and polygonal. The cytoplasm is coarsely granular and often eidophilic. The nuclei are small and spherical. Some cells are multinucleated. They resemble the cells of xanthoma, but special staining does not reveal the presence of lipid. In occasional cases cross striations have been described, suggestive of myofibrils (Crane and Tremblay: AmJPath 21: 357 1945) Three cases involving the skin of the trunk and manifested by asymptomatic nodules 1 to 3 cm. in diameter were described by Tota and Schmidt (ADS 46 225 1942) who noted the xanthoma-like cell and multinucleated strands between the connective tissue bundles of the cutis. While most cases occur in adults, those involving the alveolar processes occur chiefly in children (Bloom and Gunsler: ADS 56: 643, 1947). Cipollaro and Einhorn (ADS 56: 812, 1947) reported cases and reviewed 164 found in the literature, 62 of which were lingual, 18 from the skin, 17 subcutaneous, 13 intramuscular 11 maxillary 8 laryngeal, 8 mammary 6 mandibular 4 labial, 3 from the ear and 14 from other locations.

Two cases involving the tongue and 1 of the subcutis of the thumb were reported by Cole and Lund (ADS 60: 765 1949) They identified their cases as being closely similar to those of Fust and Custer (AmJClinPath 19: 522, 1949) who thought the lesions arose from

neurofibromas. The lesion was located near the vulva in the case of Kern et al. (ADS 61: 109 1950) in the axillary fold in that of Cornbleet et al. (ADS 63: 639 1951) and on the thigh in that of Lewis and Scott (ADS 68 86 1953)

Malignancy is of low degree and metastasis has been observed in very few cases. Malignancy occurred in those of Ravich et al. (AnnSurg 121 361 1945) Ackerman and Phelps (Surg 20 511 1946) and Powell (Arch Path 42 517 1946) quoted by Lewis and Scott. Ross et al. (Cancer 5 112, 1952) accepted as unequivocally malignant only 4 cases reported hitherto and added 3 cases they observed.

The tumors are not radiosensitive but excision cures.

See Rettter (J 76 22, 1921) rhabdomyoma of nose Abrikossoff (AfPathAnat 260 215, 1926) accredited with first description Hoff (Ztschrfkrebsforsch 39 464, 1933) nodular myolysis of tongue, Stout (AmJCanc 24 31 1938); Masson and Martin (Bassnfranc... 27 751 1938) rhabdomyoma derived from Schwannian cells, Cl att and Decourtioux (Bur-francD 46 1458, 1939) tongue case, Schmidt (ADS 45 1209 1942) histology of 3 cases Reich et al. (J 156: 714 1954) in labium major

GLOMUS TUMOR

Special organs of arteriovenous anastomosis the Sucquet Hoyer canals (q v) are found in many parts of the body but are most numerous in the tips of the fingers and toes. Occasionally one of these structures undergoes benign neoplastic change resulting in the formation of a tumor (Masson LyonChir 21 247 1924) The lesions occurring by predilection on the extremities, the fingers and even beneath the nail, are small, rounded, pinkish or purplish, fleshy nodules, composed of convoluted vascular channels surrounded by smooth muscle cells among which nerve filaments are intertwined



Figs. 1518 and 1519—Glomus tumor near olecranon. (Lewis and Geschickter J 105: 75, 1935)

The epithelioid cells have been cultivated in vitro manifesting a discrete habit small cell body and many branching processes so that they were considered to be pericytes by Murray and Stout (AmJPath 18: 183 1942) The tumors occur where pericytes are found and they may occur in places where glomera are not found. The histologic structure is variable as to proportions of the constituent muscle nerve and epithelioid cells present.

Glomus tumors are remarkable in giving rise to violent and excruciating pain paroxysmally on manipulation or trauma They develop in size only to a certain point then remain stationary Love (PSMMC 19 113 1944) stressed the fact that pinpoint pressure elicits pain at an exact spot and does not do so 1 cm distant. Pain may be such that an extremity suffers severe disuse atrophy and weakness, as in the girl reported by Oberdalhoff and Schütz (Chirurg 22 145 1951) Painful subcutaneous nodule is an old name for the condition (Wood EdinMJ 8 283 1812 Greig EdinMJ 35 565, 1928)

Patients are occasionally seen with multiple lesions there were 48 tumors in the 35-year-old woman seen by Weidman and Wise (ADS 35 414 1937) 2 patients with multiple lesions were described by Bergstrand (AmJCanc 29 470 1937) and a great many lesions, only 2 of which were painful, were disseminated in the skin of a woman seen by Eyster and Montgomery (ADS 62 893 1950) Involvement of 4 members of 1 family was noted by Kaufman and Clark (AnnSurg 114 1102 1941)

The lesions are to be differentiated from endothelioma angiosarcoma perithelioma and other tumors of greater malignancy Subungual lesions may be embedded in a depression within the bone of the phalanx, demonstrable by radiography (Ostrowski ActaMedOrient 2 142, 1943 Martorell Angiol 1 451 1950)

Painful nodules (tubercula dolorosa) were discussed by Stout (AmJCanc 36: 25 1939) spontaneous pain being sometimes observed not only in glomus tumors but also in leiomyomas, fibromas, neurofibromas, fibrosarcomas, keloids and dermoid cysts.

Excision is curative. The lesion may be tiny and hard to find, so that excision is not necessarily easy to perform



Figs 1520-1523.—Histologic structure of 3 cases of glomus tumor (Grauer and Burt J 112 1806, 1939) Fig 1520 (upper left) shows proximity of glomus units to skin of a preputial lesion of a 6-year-old boy Fig 1521 (upper right) shows intimate relation of glomus cells to endothelial cells lining Sucquet Hoyer canal. Fig 1522 (lower left) shows glomus tumor lobulation. Fig. 1523 (lower right) illustrates glomus cells, several layers in thickness, close-up appearance, from another penile lesion of adult

See Barré and Masson (BSocfrancD 31 148, 1924) Masson and Gery (AnnAnatpath 4 153, 1927) Grant and Bland (Heart 15 385, 1931), functions of arteriovenous anastomoses, histology; Lewis and Pickering (Heart 16 33, 1931) glomus function, Masson and Weil (BGO 13 807 1934) 25 cases, review, Stout (AmJCanc 24 255, 1935) 72 cases, review; Rahman and Mayer (ASurg 38 911, 1938) 3 cases; Lewis and Geschickter (J 105 775, 1935, 17 cases, Bailey (AmJPath 11 915, 1935); Geschickter (InternatClin 2 Ser 46 1 1936) review of 79 cases; Cole and Broob (J 107 428 1936) case on fifth finger, Radasch (APath 24 615, 1937) 4 of 80 cases multiple; Seapharn and deTakats (AIntM 60 823, 1937) Freudenthal et al. (BJD 49 181 1937) the glomus and tumor Theus (ASurg 34 1, 1937) in patient with peripheral vascular disease Slepyan (ADS 36 77 1937) cured 2 by excision; Meyers (JMichSMS 38 204, 1939) 4 in digits, 1 in thumb Davies et al (BJD 51 312, 1939) 6 cases Grauer and Burt (J 112: 1806, 1939) 2 cases, penile Navarro (BMJ 2: 416, 1940) sensitive to temperature changes; Foulkes and Pepple (SouthMJ 33: 268, 1940), 2 cases Blanchard (CanadMAJ 44 357 1941) 4 cases lacking muscle tissue Slepyan (ADS 50 179 1944), multiple lesions on extremities, some not painful; Meyerding and Victory (AlbanM 10: 150 1947) 2 cases cured; Stout (JMoMA 44 501 1947) pericytoma Wilkinson (BJD 62 129 1950) multiple, bluish on legs, painful only if prodded; Schneider and Eisenlohr (DWchr 121 228, 1950), 3 cases, 1 familial, and review, Allen and Dahlin (PSMMC 29 479 1954) stomach cases like those of Kay et al. (Canc 4 726, 1951)

NEURAL TUMORS IN THE SKIN

Tumors of the peripheral nervous system, rare and, generally speaking, a confusing lot variously interpreted and scattered through several medical specialties, were brought into order by Stout (JMoMA 46 255, 1949) He discussed the versatility of nerve sheath cells, which permits them to form even bone cartilage fibrotic tissue striated muscle and fat. Neurotumors, being derived from undifferentiated neuroectoderm, may partake of the characters of its different derivatives Schwannian elements and their variances, tumors reproductive of developmental stages of the sympathetic system, and rare tumors producing the embryonic appearance of the ganglionic cells of the central nervous system Neurofibroma and neurilemmoma have been established as Schwannian neoplasms by tissue culture. Malignant Schwannomas are spindle cell tumors distinct from fibrosarcomas. Stout's classification was as follows

- TUMORS OF PERIPHERAL NERVES
  - Non Neoplastic Traumatic and Amputation Neuromas and Spontaneous Neuromas
  - Neuroectodermal Neoplasms
    - Ganglionic cell tumors
      - Ganglioneuroma
      - Neuroepithelioma, undifferentiated or with rosettes
      - Medulloblastoma
      - Medulloepithelioma
    - Supportive tissue tumors
      - Neurofibroma, simple or with metaplasia
      - Neurilemmoma
      - Malignant schwannoma, simple or with metaplasia
      - Pigmented mole
      - Melanoma
  - Tumors Composed of Multiple Tissues Including Nerve Tissue
    - Glomus tumor
    - Leiomyoma
  - Tumors Associated with von Recklinghausen's Disease
    - Fibroma molluscum
    - Adenoma sebaceum (multiple)
    - Lipoma
    - Elephantiasic hypertrophy
  - Secondary Neoplasms, Including Intraneural Invasion or Metastasis
- TUMORS OF SYMPATHETIC GANGLIA
  - Ganglioneuroma Undifferentiated or Pa tly Undifferentiated
  - Sympathicoblastoma (Neuroblastoma) Undifferentiated or With Pseudorosettes
- TUMORS OF PARAGANGLIONIC CELLS
  - Phaeochromocytoma, With or Without Hormonal Activity

Amputation Neuroma.—When nerve fibers are cut degeneration is followed by outgrowth of filaments through the nerve sheaths, and an intertwined mass results if obstruction is met at the terminus. Such lesions account for the tender points and paresthesias not unusual in scars. When a scar is painful, it generally is so in only a small place which may be excised (Kredel SoCarolMAJ 35 299 1939; König DMedWehn 64 1672, 1938)

Neuroma.—The lesions are discrete, sharply defined, pea-sized tumors which are firm and elastic to the touch. After existing for many months or years, they generally become sensitive and more or less painful, and occasionally they are the seat of violent paroxysmal pain.

The majority of the patients have been middle aged or elderly men, and the lesions have been irregularly distributed over the shoulders arms and thighs pinkish or reddish in color and firmly embedded in the dermis. In the case of Duemling (ADS 19: 220, 1929), the lesion was a rapidly forming tumor of the skin, clinically resembling a keloid. It was made up of connective tissue bundles which surrounded bundles of medullated nerve fibers. In the patient of Lady (ADS 1 419 1930) a 37 year old Negress, the lesions were painful and had been mistakenly thought tuberculous they resembled the lesions of prurigo nodularis. A large tender plaque diagnosed neuroma by biopsy developed on a woman's breast following an abscess of the nipple (Senear et al.: ADS 52: 202 1945). Shiny smooth, flesh colored, discrete and coalescing nodules affected a young man's eyelid, having appeared 10 years previously, in the case of Epstein (ADS 60: 1037, 1949) and the microscope showed sharply demarcated bundles of tissue resembling that of amputation neuroma, without palisading

Neurilemmoma.—Synonyms for the specific tumor of the nerve sheath tissue include, according to Stout (AmJCanc 24 751 1935) neurinoma (Verocay BeitrPathAnat 48 1 1910) schwannoma and peripheral gli oma. Compare nevus cell tumors, which are often, at least in part, of Schwannian origin. The tissues of neurinoma are well differentiated and dif ferent from those of fibroma and neurofibroma. They have long been recog nized when found attached to spinal nerve roots or the intracranial portions of cranial nerves. They are benign and movable except for their attachment to the nerve sheath from which they arise There is no sex or age predilection. They occur by predilection at the flexures of the arms and wrists, sides of the neck flexures of the knees and ankles, on the tongue in the wall of the stom ach, along the aorta and the intestines, rarely on the trunk. Excision is cura tive

These tumors are composed of reticular tissue in bands, the cells resembling those of Schwann, in areas reproducing organoid structure suggestive of Meissner s tactile corpuscles. Small intradermal tumors closely resemble nevi; in fact the hemispherical, colorless, firm, smooth nevi are often of this type. The tongue is a relatively common site. A palatine lesion was reported by Seltzer (MRec 131: 203 1940) They occur along the gut (Hanson and Kay: AnnSurg 112: 700 1940), and in the mediastinum. Some authors have believed that the lesions of Recklinghausen's disease are not of connective tissue origin, but that the fibers are nerve fibers and the cells are sheath cells of Schwann (Becker: ADS 30: 799 1934)



Fig. 1524.—Neurinoma of girl' cheek.



Fig. 1525.—Neurinoma f tongue.

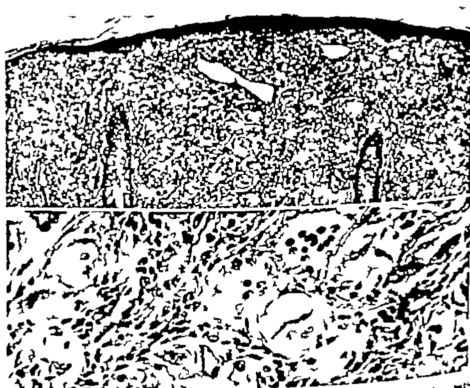
The capabilities for differentiation of the neuroectodermal cells migrating from the neural crest are indeed various (Stone: AfEntwicklungs 118 40, 1929) Schwannian cells produce reticulin when grown in vitro (Murray and Stout: AmJPath 18: 585 1942) Schwannian tumors are said t be capable of producing bone, cartilage and fat (Groth: ActaPathMicrobiol 11: 44 1934) They may produce tumors composed of tactile corpuscles (Worster-Drought et al.: Brain 60: 86 1935); such cases have been described by Foot (APath 30: 772, 1940) A bean-size congenital tumor of a man's finger was histologically a mass of pacinian corpuscular tissue (Cammermeyer: APath 4 : 1 1946) and 2 histologically similar benign lesions resembling nonpigmented nevi were reported by Prichard and Custer (Canc 5: 297 1952) See Pigmentary nevus regarding the contribution of neural crest tissue to nevus structure. See also Neuroma.

See Duhring (AmJMedSci 66 413, 1873 82 436, 1881); Heidingsfeld (J 60 498, 1913); Foot (APath 30: 772, 1940); Saxen (ActaPathScand 25: 66, 1948) pacinian tumors.

RETICULOHISTIOCYTOMA

This name was used by Allen (ADS 57 54 1948) to designate 2 cases resembling ganglioneuroma, and Zak (BJD 62: 351, 1950) reported 4 more, 3 of which seemed identical with the ganglioneuroma of Montgomery and O Leary (ADS 29: 26 1934) The remarkable large pale cells, stellate and with 1 or more vesicular nuclei and prominent nucleoli, were present in places overshadowed by a banal inflammatory infiltrate. The histologic structure

Fig. 1526.—Reticulohistiocytoma, showing nodular lesions on hand and ganglion on each wrist. (Caro and Senear, ADS 65: 701, 1952.)



Figs. 1527 and 1528.—Reticulohistiocytoma, lesion from papules on [illegible] of patient different from that shown in Fig. 1526. Fig. 1527 (above) shows densely packed giant cells. Fig. 1528 (below) shows [illegible] giant cells containing many pale nuclei and dark nuclei amid connective tissue. (Drs. Marcus A. Caro and F. E. Senear.)

distinguished the lesions from those of xanthoma, benign giant cell tumor and amelanotic melanoma. Two cases showing respectively nodules on the hand and small papules on the ears were studied by Caro and Senear (ADS 65 701 1952) who distinguished reticulohistiocytoma from ganglioneuroma by staining with thionine blue which demonstrates Nissl granules in ganglioneuroma absent from the histiocytic disease, wherein there occur lesions resembling the nodules in rheumatoid arthritis but differing in that they are composed of masses of bizarre, multinucleated giant cells. The relationship of the cutaneous lesions to arthritis was emphasized by Goltz and Laymon (ADS 69 716 1954) who reviewed the literature and added 2 cases The disease seems to be related to but distinct from benign synovial and tendon sheath tumors, eosinophilic granuloma, the odd xanthomatoses, and erythema elevatum diutinum. Caro and Senear (ADS 66 630 1952) noted that the disorder had been described previously by Weber (ProcRoySocM 30 622, 1937 BJD 55 1 1943) and others, the association of multiple cutaneous nodules, juxta articular infiltrations and rheumatoid symptoms having not been overlooked. The disease was evidently seen by Crocker (Diseases of the Skin Blakiston, 1906 p 1024) who called it myeloid cell sarcoma the patient was a man whom he exhibited in 1896 and whose lesions began on the hips and spread widely and disappeared, apparently after salicin was given because of his arthralgia. Purvis and Helwig (AmJClinPath 24 1005 1954) discussed the histologic features of 44 cases.

Ganglioneuroma.—A papular and nodular eruption in a 20-year-old male, which consisted of discrete round, firm, yellowish lesions ranging from 1 to 10 mm. in diameter and appearing first over the buttocks and spreading to the pubes, abdomen, axillae back and neck, with a small scattering elsewhere, was reported by Montgomery and O'Leary (ADS 29: 26, 1934) The lesions gave rise to a pricking sensation on pressure. Histologically the predominating cells of the early nodules were large pale-staining and possessed of the outstanding morphologic features of sympathetic ganglion cells: they contained 1 or 2 densely staining nuclei and had fine Nissl granules in the cytoplasm and supported multiple dendritic processes. The disorder certainly wa not xanthoma or tuberculid.

PILOSEBACEOUS ADENOMAS

Adenoma Sebaceum.—The lesions are of pinhead to split pea size, yellowish in color and usually distributed in a symmetric manner over the nose cheeks and nasolabial folds. They are long benign but persist indefinitely They seldom, if ever develop into basal cell carcinomas. Familial incidence is often noted. Adenoma sebaceum is sometimes associated with tuberous sclerosis, mental deficiency and convulsions (Koon and Williams ADS 50: 96 1944) Pringle s syndrome (BJD 2 1, 1890) comprises the combination of these lesions with subungual and periungual warty fibromas. The relationship of tuberous sclerosis with adenoma sebaceum is not mere coincidence. Sherlock (The Feeble Minded Macmillan 1911) gave the name epiloia to the complete syndrome of mental deficiency epilepsy and adenoma sebaceum and he described 9 cases.

I epiloia, the onset f convulsions almost always precedes the appearance of the sebaceous gland anomalies (Ross and Dickerson: ANeurol 50: 233, 1943) *Formes frustes* are seen, and epiloia may be associated with other ectodermoses such as neurinomas, neurofibromas nevi pigmented spots and the like (Butterworth and Wilson: ADS 43: 1 1941) Adenoma sebaceum of Pringle was clearly distinguished from epithelioma adenoides cysticum f Balzer by Artom and Cerruti (abs YBD 1946, p. 297) The lesions of the former are smaller vascularized, soft and fleshy centrally located on the face associated with other nevi, and with *formes frustes* of Recklinghausen's disease, rarely familial, histologically constructed f vessel and connective tissue hypertrophy sometimes containing sebaceous glands and never undergoing malignant degenerat on.

In epithelioma denoides the lesions are whiter and firmer are irregularly located on the face and not ssociated with nevi or with central nervous system disease, are usually familial, are constructed of epidermal adnexal tissue, and commonly undergo basal cell carcinomatous progression, as in cases of Sharlit (ADS 51: 56, 1945) and Schamberg (JCutD 27: 170 1909; 29: 500, 1911) See also Nevus sebaceus and Hypertrophic fat gland.

TREATMENT —The lesions sometimes respond well to applications of solid carbon dioxide. Various modalities for performing nice destruction can be used to remove them they are benign.

Tumorlike and cystic lesions of the face in the patient of Lobitz and Cole (ADS 66 358 1952) were reduced in size by large doses of estrogenic substance but they did not respond until after hyperplasia of the breasts began.

See Rayer (Diseases of the Skin, Willis transl Philadelphia, 1835, pl. 14, fig. 8), "vascular vegetations", Addison and Gull (GuyHospRpt 8: 267, 1852); Balzer and Ménétrier (ArchdePhysiol 6 564, 1885) named the lesions "adenoma sebaceum", Balzer and Grandhomme (ArchdePhysiol 8: 93, 1886) association with tuberous sclerosis Barlow (DeutM KlinM 55 61, 1896); Unna (Histopathology Macmillan, 1896, p. 814); Pollitzer (J 15: 174, 1901); Crocker (Diseases of the Skin, Blakiston, 1908, p. 1111) Vogt (MonatshPsychNeurol 24: 106, 1908) Pringle's syndrome; Sutton (JCutD 29 480, 1911) differentiation of adenoma sebaceum and epithelioma adenoides cysticum Shelmire (J 71: 963, 1918), 8 aths, CO_2 therapy; Crutchfield (ADS 2 388, 1920) case with also Wilms' tumor, Rosen and Wolf (ADS 1: 13, 1920) case, defective child Sephler and Klendl (UCutRev 25 271, 1921) Nurera (GiornItalmalven 65 344 1924) histology, Fuhs (AfDuS 148, 509 1924 1925); Ertner (WienKlinWchschr 39: 242, 1926); Truffi (GiorItalD 67: 464, 1926) Delmond and Schwartzmann (BaoctreagD 46: 406, 1930), familial Roncheese (ADS 23 792, 1931) case, Pringle' Critchley and Earl (Brain 55: 311, 1932) formes frustes but no association with Recklinghausen's disease, Parounagian (ADS 31 420 1935) notable periungual involvement; Gilman (ADS 35: 611, 1937) wax model Carol and Heusden (AfDuS 175 1, 1937), Bourneville-Pringle's syndrome, James (Lancet 1 1222, 1937) epiloia Walsh et al. (PEDMC 13: 185, 1938) retinal tumor too Messinger and Clark (AOphth 18: 1, 1937) 25 cases collected of associated retinal glioma Kawamura (J pJD&U 44: 91 1938) Bourneville-Pringle phacomatosis Urbach and Weidman (AfDuS 158 334, 1929) father and 6 of 11 children with Pringle's disease, 5 sisters with tuberous sclerosis and 1 with neurinoma, discussion of relation with Recklinghausen's disease Bamber (BJD 52: 258 1940), case Quill and Marting (Surg 9, 541, 1941), 7 cases of epiloia in 3 generations of a family, all with nail bed lesions Woolhandler and Becker (ADS 45: 734, 1942) varieties of fat gland abnormality Pinkle (ADS 48 198, 1943), good results with CO_2, Sachs and Shaskan (AmJRoentg 52 38, 1944) case, Pringle' ; Carney (ADS 64 506 1951) astonishing case, nose and chin lesions resembling frog spawn.

Epithelioma Adenoides Cysticum is characterized by pinhead to pea-size rounded, shining translucent nodules which exhibit a predilection for the face where they may be few or numerous and are more or less symmetrically *disposed and centrally located They are of firm consistency and give rise to* no symptoms. They are generally discrete, but may be closely bunched. Telangiectasis is an accompanying feature about large lesions. A familial tendency is frequently noted. While usually numerous, solitary lesions are seen. They begin as tiny papules which gradually develop up to a certain point where they remain stationary On the face the distribution is often more or less symmetric, but on other parts of the body this tendency is absent.

When malignancy supervenes, as it *sometimes does* waxy nodules of basal cell carcinoma develop slowly progress and ulcerate with variations in rate of growth. It is probable that many basal cell carcinomas start as solitary accessory structure hamartomas of the epithelioma adenoides cysticum sort, remain benign for years perhaps suffer trauma at the hands of the patient who mistakes them for comedones or milia and then grow progressively

The clinical picture produced by the spontaneous and more or less simultaneous progression of each of many lesions into a firm pinkish nodule of basal cell carcinoma, which eventually ulcerates, is a striking one (Sutton J 115 2256 1940 ADS 42 838 1940) See Adenoma sebaceum Syringocystadenoma Basal cell carcinoma.

Pigmented lesions, called basal cell nevi were the source of origin of pigmented basal cell carcinomas (q v) in the unusual case of Nomland (ADS 25 1002, 1932)

ETIOLOGY AND PATHOLOGY —The lesions represent dysontogenesis of the hair apparatus. Women are affected more frequently than men. The lesions commonly become apparent about the age of puberty Histologically the papules are composed of organoid congeries of basophile epidermal cells, the arrangement of which parodies the pilosebaceous apparatus.

The histologic study by Savatard (BJD 34: 381, 1922) accompanying his case report, was admirable; he suggested the title follicular nevi. Ingels (ADS 32: 75 1935) made a wax model reconstruction which showed all downgrowths to be in continuity with the epidermis or hair follicles. He believed that epithelioma adenoides cysticum, trichoepithelioma, and adenoma sebaceum are variants of the same process, while syringoma is distinct. The relation to cylindroma (turban tumor) was made apparent by the essay of Savatard (BJD





Fig 1529.—Adenoma sebaceum, associated with large fibroma of left side of scalp. (Original of Good and Clark ADS 47 197 1943, from Wiener Skin Manifestations of Internal Disorders, Mosby 1947)

Fig 1530.—Adenoma sebaceum. (Dr J Lamar Calloway)



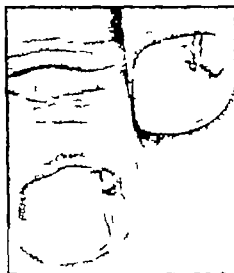


Fig. 1531.—Adenoma sebaceum. (Dr Harry E. Alderson.)

Fig 1532.—Fibromas of nail beds with longitudinal grooving of nails, in tuberous sclerosis (Original of Noon ADS 50 98, 1944, from Wiener: Skin Manifestations of Internal Disorders, Mosby 1947)

See Petersen (AfDuS 26: 440, 1893) Fick (MonatshPrakD 48: 1[illegible], [illegible], 1909) distinction from other types of epithelial abnormalities Ormsby (JCutD 28: 4[illegible], 1910) extensive distribution symmetrical on extremities Stillians (JCutD 37 55 [illegible], 1919) unusual case Saphier and Kiendl (UCmRev [illegible] [illegible], 1921), association with adenoma sebaceum and neurofibromatosis Greenbaum (AmJOphth 11 [illegible], 1928) eyelids Choraszak (PraegD 21 [illegible], 1936) generalized on trunk Sheer (ADS 55 843 1947) extensive distribution on trunk

Hydrocystoma is a benign, presumably neoplastic abnormality of sweat gland tissue characterized by discrete tense deep-seated noninflammatory vesicles occurring usually on the face and forehead. The malady a rather rare one was first described by Robinson (*JCutD* 11 293 1893 Manual of Dermatology New York 1884, p 84) The lesions occur in circumscribed



Fig. 1537 —Syringocystadenoma. (Dr P Schaffner)



Fig. 1538.—Syringocystadenoma.



Fig. 1539 —Hydrocystoma, located on forehead



Fig. 1540 —Hydrocystoma.

groups of thick walled pinhead to pea-size rounded or oval, translucent vesicles. The central areas are darker than the margins. The face particularly the sides of the nose flush areas of the cheeks, and forehead, is the likely location. The tiny cysts never rupture *spontaneously* Symptoms are slight or absent. The lesions may swell and itch when the patient sweats.

Apocrine sweat retention cysts occur as small isolated, papular lesions that can be identified histologically (Shelley et al AD 72 171 1955)

In treatment one may puncture and drain the cysts. X ray therapy will make them disappear Cryotherapy provoking exfoliation is effective

Hydrocystoma is a variable condition, in that the lesions come and go. They fill when the patient sweats and regress as a rule in the wintertime. They may recur annually in the summer months over a period of several years. Persons subject to hyperhidrosis are said to be more susceptible to hydrocystoma. The majority of the cases reported have occurred in middle-aged women, especially in laundresses. I have encountered several instances in young, otherwise healthy Kansas farmers. Exposure to moist heat aggravates the lesions in many instances provoking their appearance.

The vesicles disappeared when atropine was given and reappeared with pilocarpine in the case of Dostrovsky and Sagher (JID 5: 167 1942) Compare Syringocystadenoma; the disease is also to be distinguished from vesicular dermatitis, pompholyx, lymphangioma and, with difficulty localized miliaria crystallina. Cyst formation is the result of dilation of sweat glands and ducts, the dilation being located histologically generally just exterior to the cells of secretory epithelium. The duct is enormously distended, filled with retained sweat and lined with flattened epithelial cells.

Syringectasia due to inflammation and obstruction was reviewed by Brodoway (DWchr 105: 1157; 1180, 1937) who observed that the process occurs commonly in a variety of conditions which pathologically impede the outflow of sweat.

Cysts of the Glands of Moll are small, transparent hydrocystoma like lesions located at the borders of the eyelids. They may evolve into basal-cell carcinomas. Compare epithelioma adenoides cysticum.

Hydradenoma.—The lesion is a small, white, circumscribed, elastic, innocent looking tumor generally solitary and located on or near the vulva. The labium major is the usual site the labium minor less often being involved. The lesion is generally of long duration, for it is inconspicuous to the patient and asymptomatic. The size ranges from 3 to 20 mm in diameter with slight elevation. The age of the patient when the tumor is brought to the surgeon's attention is likely to lie between 25 and 60 years. Ulceration is quite rare. Some 40 cases were found in the literature by Rothman and Gray (AmJObGyn 38: 509 1939) Excision is curative.

When sectioned in the gross, whitish, bulging, adenoid material is seen to be apparently encapsulated. The microscope discloses bizarre, epithelium-lined clefts suggestive of apocrine or sudoral origin. A double-layered epithelium with a membrana propria about the adenoid tubules was described by Pick (AfPath 175 312 1904) indicative of sweat gland origin. The structure may be tubular adenoid or mixed, the cystic nodule containing proliferative tissue in labyrinthine or papillomatous configuration. The stroma is delicate and scanty Mucin, apparently secreted by the sweat gland epithelium, was found in the tumors by Lennox et al. (BritJCanc 6 363 1952)

Subcutaneous Papillary Cystadenoma, presumably of sweat gland origin, was described by Müller (GeneeskTijdNederlInd 76 2787 1936) in a report of 5 instances of solitary subcutaneous tumors which were as large as 7 cm. in diameter of local growth only and composed of uniform cells of basal type.

Eccrine spiradenoma was the name given by Kersting and Helwig (TransADA, April, 1955) in their study of a remarkable collection of 134 lesions, all but 2 of which were solitary The location was generally in the ventral skin none affected palmar or genital regions. Usually they gave rise to severe pain. The range in size was from 0 3 to 5 cm. Growth was slow tending to become stationary 5 years after onset which occurred at ages ranging from 15 to 35 years as a rule The distinctive microscopic structure resembled that of nodular syringoma (q v) Dark-staining peripheral and pale central cells formed an alveolar filigree surrounded by reticulum that stained as it does about the tubules of sweat glands. Connection with sweat ducts could be traced in serial sections in 2 cases.

The lesions are encapsulated and easy to remove Excision is curative.

See Burg (ZentralblGynak 54: 396, 1930) review vulvar hydradenoma; Eichenberg (ZtschrGeburtshGyn 109: 368, 1934) 13 labial cases; Schmidt (ADS 41 393, 1940), solitary syringoma on girl hip McDonald (AmJClinPath 11: 390, 1941) 30 cases Balog (ActaD-V 22 187 1941), nodular syringoma on girl thigh; Cooper and McDonald (APath 38: 166, 1944) anal case Levin and Clarke (SurgClinNoAm 24: 1172, 1944) hydradenoma comprises about 4% of tumors of female genital tract; Novak and Stevenson (AmJObGyn 50: 641, 1945) 15 vulvar cases Cunningham and Hardy (SouthSurg 13 831, 1947) 4 cases and review of 80; Sayre (PaMMC 24: 124, 1949); Anderson (ADS 62 873, 1950), interrelations of various kinds of syringoma; Wilkins and McDonald (ASurg 61 610, 1950) hydradenocyst and its role in breast cancer; Steigleder (DWchr 124: 1049 1951) 6 cases of syringoma.



Fig. 1841.—Hydradenoma

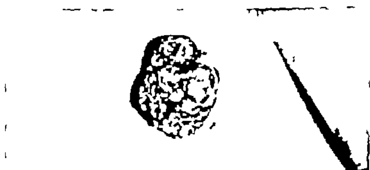


Fig. 1842.—Nevus syringocystadenomatosus papilliferus, in which squamous carcinoma has intervened. (Dr. F. Bonchese.)

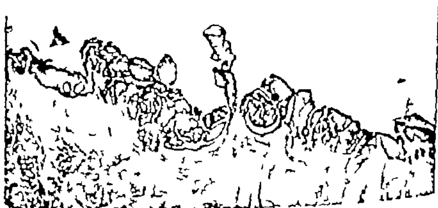


Fig. 1843.—Nevus syringocystadenomatosus papilliferus, showing papillomatous proliferation of sweat gland epithelium and adenomatous dilation of the sweat gland. (From the collection of Dr. Frieboes, in McCarthy: Histopathology of Skin Diseases, Mosby, 1931.)

Nevus Syringocystadenomatosus Papilliferus.—These rare lesions are papules or nodules usually of small size sometimes arranged in groups. They are pinkish but translucent and vesicular inclusions may be detected. Some papules are umbilicated, simulating molluscum contagiosum. Isolated lesions occur but often they are confluent and the plaques may be of considerable area or systematized (Elliott JCutGUDis 11 168 1893) The shoulders axillae genitocrural folds and scalp are the sites of predilection. Excision is curative.

Microscopically one finds the sweat ducts cystic and papilliferous, emptying onto the surface through thickened epidermis (Sachs and Lewis ADS 36 1202 1937) The dermis is permeated with nevus cells. The digitations which push into the dilated sweat ducts support an inner columnar and outer cuboidal layer of sweat duct epithelium, which rests on delicate connective tissue of a structure analogous to that of the papillary layer of the dermis. The lesions are not inflammatory unless secondarily infected. Plasma cell infiltration may be more or less profuse See meticulous histologic study of Beerman (ADS 60 500 1949)



Fig. 1644.—Multiple benign epitheliomas of the scalp, "turban tumors." See Fig. 1645. (Roschmann: AmJCanc 18 873, 1933.)

See Syringoma, Cylindroma. See Rolleston (BJD 14 43, 1902) case; Werther (AfDuS 116 665, 1913) origin of the name; Stokes (JCutD 35 411 1917) case, Frieboes (Histopathologie der Hautkra kh., Vogel, 1921, p. 166); McCarthy (Histopathology Mosby, 1931 p. 366) description, bibliography; Reuterwall (ActaPathScand suppl. 16, p. 131); Fessler (DWchn 94 650, 1933) case; Dörffel (DWchn 99 1316, 1934; 100) 229 1935), excised lesion of sweat gland structure recurrence w of sebaceous structu ; Nodl (AfDuS 170 697 1935) 3 cases Müller (GeneeskTijdNederland 76 2767, 1936) 6 cases of solitary subcutaneous tumor as large as 7 cm diameter Y masaki (abs ADS 46 740, 1942) case, Mondor and Gauthier Villars (PresseM 54 339 1946) case Prakken (Dermatologica 96: 436, 1948) case; Perel al (ArchBelgD 4 95, 1948) case, histology Marcus and Woodriders (ADS 61 105, 1950) case combined with sebaceous nevus; Appel (ADS 61: 211 1950) large lesion in groin Mears (BJD 63 112, 1951) case; Grund (ADS 65 340, 1952) case, scalp, with features also of sebaceous nevus; Pinkus (ADS 69 305, 1954) lit history of this tumor

Cylindroma (Turban Tumor) is included within the class of neoplasms of local activity which arise from sudoriferous anlagen and progress to form smooth rounded nodules of from pea to walnut size Such nodules in groups are of more common occurrence than is their solitary appearance Their situation in numbers on the scalp gives rise to a condition described as turban tumor interpreted as endothelioma capitis by Kaposi.

Turban tumors are not always of the same structure; they may be trichoepitheliomas in some instances. Savatard (BJD 50: 333 1938) thought them variants of the same condition as epithelioma adenoides cysticum. If the hyperplastic tendency may instigate proliferation of the lesions from surface

epithelium or from hair as Savatard insisted, it may with equal likelihood provoke their origination from sweat gland. I prefer to think that distorted organization results in tumors, rather than that tumors spring from pre-existing structures with similar organization and so insistent on their epithelial

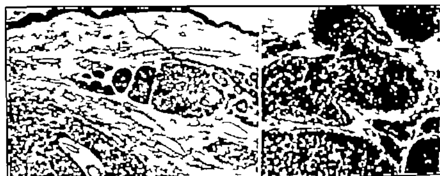


Fig 1545.—Multiple benign epithelioma sections of lesion shown in Fig. 1544. (Borchers AmJCanc 18 875, 1933.)



Fig. 1546—Nodular syringoma, or "turban tumor" involving the neck, unilaterally. The lesions on the cheek were n us cell tumors. Neck lesions, present since childhood, were slowly enlarging. Photomicrographs show Above an isolated sweat gland lobule overlying one nodule, representati of syringectasia below numerous small, dark strands of cells surround a central adenoid tubule. See Fig. 154

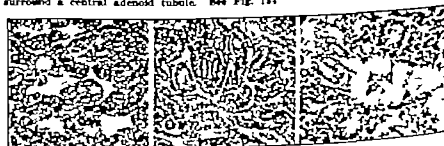


Fig. 1547—Several regions of the tumors show in Fig 1546. Note, t right, peculiar isolated group f mucou gland ( ) acini, which ha been described, but not emphasized, in other cases of syringoma (Sutton ADS 30 193, 1934.)

origin, I am indifferent as to the point of apparent attachment or adjacency of tumor cells with normal ones, a mere relationship of space. The cell masses, having arisen, differentiated and organized so as to resemble syringoma, may with justification be called syringoma

Sweat glands, hairs and other structures differentiate from a common stem, and so presumably do the organoid lesions of epithelioma adenoides cysticum, sebaceous adenoma, syringoma and like abnormalities. Ronchese (AmJCanc 18: 875 1933) interpreted turban tumors as simple multiple, benign epitheliomas; Hval (ActaD-V 17: 1, 1936) considered them sweat gland nevi. Sutton and Sutton (ADS 30: 194, 1934) described a case involving the neck unilaterally like that of Homma and Escher (ADS 33: 700, 1936) Nékám, finding no myoepithelium in sections from our patient, denied a sweat gland origin. Wiedmann (AfDuS 169: 180 1934) described the lesions in 4 generations of 1 family Adamson (BJD 30: 130, 1918) thought them basal cell carcinomas and, in review could locate only 3 acceptable cases of true sarcoma involving the scalp, which Crocker had thought the tumors to be. They were called "Spiegler's cylindroma" by Schuermann and Weber (AfDuS 175 682 193?) 1 of whose 18 collected cases had many large tumors of the back. The origin in sweat glands was championed by Friboes, in hair follicle by Schlammadinger Blakley (ADS 37: 290 1933) named them "Nevus epitheliomatocylindromatosus" discussing Blakley's cases, 1 of which was squamous carcinoma in a wen, Weidman thought the lesions trichoepitheliomas. A typical case was shown by the patient of Jones et al. (ADS 26: 659 1932) a woman with 200 or more tumors in the scalp. The lesions are not necessarily limited to the scalp in distribution, and may be solitary as in the patient reported by Eljas (ActaD-V 16: 423 1935) A father and daughter were affected the daughter showing also epithelioma adenoides cysticum, as reported by Graul (DWchn 123: 949 1933)

I attribute the nodules to proliferation of sheath cells of sweat tubules. These cells Lever (ADS 57: 332, 1948) judged to be myoepithelial, and for such tumors he recommended the name myoepithelioma. Large foam cells are occasionally seen within the nodules in discrete groups, conspicuously different from the majority of the cellular components of the lesions, they were noted by Dies and Peterschmidt (BSocfrançD 184 599 1926) and in our case. Perhaps they are the same as those of granular cell myoblastoma. The myoepithelium of the sweat gland was thought to be the origin of 3 little tumors, of which 1 from the toe behaved like a malignant melanoma, described by Sheldon (APath 31 326, 1941)

Compare apocrine cysts of th scalp (p. 1171)

The onset of the lesions is generally between the ages of 14 and 80 and they reach their full development at from age 50 to 70 (Ronchese) Growth is slow and their behavior is generally benign, although some lesions grow as basal cell carcinomas. They may be excised with the expectation of cure which cannot otherwise be achieved but an extensive case would be a challenge to the plastic surgeon.

See Dubreuilh and Auché (AnndeD 4 345, 1903) recognition of "endothelioma capitis" as accessory structure epithelioma; Lemaître (Étude anatomoclinique des tumeurs dites cylindromes, Vigot, 1937) 192 pp illustrated monograph; Wendlberger (AfDuS 176 407, 1938) pathogenesis; Eaton (ADS 40 948, 1939), case developing after trauma, called "naevo-epithelioma adenoides"; Chevrel-Bodin (BSocfrançD 47 76, 1940) case, "Ricker and Schwalb multiple, hyaline, sudoriparous epitheliomas"; Shepard (ADS 45 105, 1942) involving scalp and face Cooper (J 122 878, 1946) involving trunk and scalp; O'Leary et al. (ADS 62: 614, 1950) simulating Recklinghausen disease Colovras and Gery (J 147 784, 1951) turban tumor; Smith (ADS 66: 737 1952), nodules on left shoulder; Costa (Dermatologica 105 184 1952) turban tumor; Evans (BJD 66 434, 1954), plastic surgery in 2 cases, structure suggested nevoid deformity of tissues originally destined to become apocrine gland.

SEBACEOUS AND SUDORAL NEOPLASMS

Tumors of Sebaceous Glands, other than hypertrophic fat glands, nevus sebaceus, adenoma sebaceum and sebaceous adenomas (q v) are uncommon. Sebaceous carcinomas clinically resemble basal cell carcinomas. They are diagnosed only by histologic examination, which reveals the unforgettable picture of sebaceous cells in neoplastic arrangement, in all stages of evolution. Among 4 000 skin neoplasms reviewed by Warren and Warvi (AmJPath 19 441, 1943) 20 were called sebaceous carcinomas they were of slow growth and late to ulcerate They are locally invasive and have been known to metastasize One seen by Sweitzer (ADS 54 583 1946) appeared superficially to be a squamous cell lesion; deeper it was of sebaceous structure. Interestingly the sebaceous gland of the external auditory meatus in the rat (Zymbal's gland) frequently undergoes neoplastic proliferation, the cells of the expansive tumors assuming both squamous and sebaceous features, when the carcinogen 2-acetylaminofluorene is administered for the purpose of inducing carcinoma of the liver (Laws et al. CancRes 15: 139 1955)

Sebaceous Adenoma occurring as a solitary organoid tumor sharply demarcated, composed of adenoid lobules and containing both differentiated and

undifferentiated sebaceous cells, is occasionally seen (Lever ADS 57 102, 1948) Clinically it resembles a basal cell carcinoma but is yellowish, with a bosselated surface. This uncommon tumor was briefly reviewed by McMullan (AD 71 725 1955) who preferred the name sebaceous epithelioma.

Adenocarcinoma of the Ceruminous Glands is indeed exceptional. The structure in the cases of Montpellier and Laffarque (Bassmfrançétudecancer 27 774 1938) resembled that of the normal gland and of the mamma 1 of them came from a man and the other from a cat. A case in an old man penetrated the auricle and caused facial palsy reported Warren and Gates (AmJPath 17 821 1941) who reviewed the literature accepted 3 cases and judged 7 others probably acceptable.

Tumors of Sweat Glands include syringocystadenoma (q v) papilliferous hydradenomas of the vulva usually occurring as solitary well-encapsulated, white firm slow growing lesions and papillary and solid types of carcinoma resembling basal cell lesions, according to Gates et al. (AmJPath 19 591 1943) Cases of sweat gland carcinoma ranging from tubular adenoma structure to that of squamous carcinoma, were found in the nipple, cheek forehead and upper lip of 4 patients by Flarer (AnndeD 6 1071 1935) In 3 cases from *the ear and 1 from the temple of elderly men,* Lever (ADS 56 157 1947) depicted structure resembling that of a squamous carcinoma of low cohesiveness and adenoid array of its plexiform sheets. See Loos (AfDuS 174 465 1936) Dupont (ArchBelgD 3 275 1947) Lopez and del Pozo (abs BJD 61 306, 1949) Kaplan (ArchOtol 56 250 1952) Stout and Cooley (Cancer 4 521 1951) were able to collect 6 cases of metastasizing sweat gland carcinoma and 5 without metastases, and they found in the literature 7 cases of metastasizing sweat gland carcinomas. The tumors tended to grow within the skin, generally in elderly persons, and the favored sites were those where apocrine glands are normally found. The tumors were reddish or violaceous and could be diagnosed only by biopsy Metastases were to regional lymph nodes. Three *original cases and 47 others of the clear cell hydradenoma* type of sweat gland adenoma were reviewed by Keasbey and Hadley (Cancer 7 934 1954) and 2 of the 50 metastasized to the bones and lymph nodes, proved radioresistant, and were fatal.

Tumors of the Apocrine Glands were said by Gates et al. (AmJPath 19 591 1943) to be very rare located as a rule at the anus or on the vulva. None on record has been malignant. A tumor of the ciliary gland of Moll was reported by Hagedorn (KlinMonatshAugenh 96 171 1936) Perianal lesions representing carcinoma of mucous glands or perhaps of apocrine tissues were described by Whimster (Hautarzt 4 40 1953) See apocrine cysts of the scalp (p 1171)

Carcinoma of Bartholin s Gland may be adenoid or squamous, and is first noted as a small, hard painless nodule deep in the labial fat, movable at first but becoming fixed tending to grow deep resembling an abscess and causing pain in the coccyx and groin with dyspareunia according to Simenlinger (SGO 68 952, 1939) who added 18 cases to those collected by Falls (AmJOb Gyn 6 673 1923) The lesions metastasized first to the inguinal nodes. The average age of the patients was 51 6 years.

CUTANEOUS FISTULAS SINUSES AND CYSTS

There are several sites on the surface of the body where improper embryologic development results in incomplete closure of a fold or invagination, or incomplete resorption of an epithelial tract (Mount J 179 1953, 1919) Lesions of this origin include branchial cysts and sinuses, and sacral and coccygeal cysts and fistulas. Failure of closure results in fistula formation, partial closure in cystic lesions, incompletion in dimpling these manifestations

representing various degrees of defect. A review with bibliography of cysts of epidermal and other origin (sebaceous, synovial sweat duct, traumatic, mucous, dermoid) and of sinuses and fistulas was given by Anderson (J 135 607 1947)

Pilonidal Cysts and Sinuses are sometimes demarcated on the skin by the presence of a hairy pigmented mole a dimple or a crusted papule. Sinuses may open in the median line over the lower sacrum or coccyx. Sinuses in higher cord segments occur but are rare. They may even penetrate the meninges, and the symptoms of some cases include recurrent attacks of meningeal irritation or inflammation. The sinuses are lined with squamous epithelium. They extend upward in a sometimes erratic and difficultly discoverable course even within the sacrococcygeal joint itself They often coat in hair in a terminal pocket an inch or 2 from the orifice. Cysts and abscesses readily occur The best treatment is probably that of Marks (SouthMJ 40: 844, 1947) which consists in laying open the tracts and suturing their lining to the skin.

See Mallory (AmJMedSci 103: 263, 1892) 19 cases, review Weeder (AnnSurg 93: 285, 1933) involvement of sacrococcygeal joint Owen (SurgClinNoAm 14 117 1934) only 2 of 40 cases affected females Walker and Bucy (Brain 57 401, 1934) fistula extending into cord t fourth dorsal level, review of spina bifida occulta Edit (J 103 1786, 1935) sinuses, bibliography, Iredenbach and Wilson (AnnSurg 101 488 1935) 233 cases, Ravdin and Johnson (AmJMedSci 190 260, 1935) sacral dimples in 2.6% of 1040 males Goldberg (J 112 1401, 1939) in identical twin infants Gage (AnnSurg 109 291 1939), embryology; Rogers (NEngJM 222: 18, 1940) surgical technic Tendler (SouthMJ 34 1166, 1941)

Sinuses Communicating with the Central Nervous System.—Such congenital dermal sinuses are rare, but have been known to result in fatal meningitis (Cardell and Laurance: BMJ 2: 1558 1931) The lesion consists of an epithelial tube extending inward from the skin of the midline of the back t connect with the central nervous system or its coverings. The sinus orifice i often associated with a tuft of hair an area of pigmentation, or a capillary hemangioma. It is lined with epidermis, with o without accessory structures, histologically like the common pilonidal sinus, differing only in location. Cases have occurred in all sites between the occiput and the sacrococcygeal region.

Coccygeal Fistulas are congenital defects occurring usually in the male only in th white race sometimes familial, and often i association with other developmental anomalies (Stone: AnnSurg 79 410 1924)

Perianal Cysts.—I the development of the caudal parts, complex changes involve the medullary tube primitive gut, notochord and cloaca. Cloacal vestiges found i the anorectal canal, giving rise to anal glands, are common sources of fistulas, fissures and perirectal abscesses, as well as of caudal gut and cloacal cysts (Gius and Stout: ArchSurg 37 268, 1938)

Perineal Fistulas and Cysts.—Lesions may occur along the perineal raphe from urinary meatus to anus. These may be mucous or dermoid and are subject t infection with various pathogens, including the gonococcus. See Neff (AmJSurg 31 308 1936) Wooldridge (AD 71 713 1953) Smith (J 136: 973 1948) in his report of 4 cases differentiated them from presacral dermoids, poi ting out that they cann t arise from embryonic vestiges of the neural canal.

Umbilical Fistula.—Intermittent discharge from th umbilicus with attacks of pain and inflammation may be due t a sinus representing persistence of the urachus (Wilmoth: J 106 626, 1936) See endometrioma (p. 1141)

Auricular Anomalies.—The varieties of anomalies of the ear were described by Foucar (CanadMAJ 43 26 1940) absence of the external auricle with or without middle and inner ear abnormalities ectopic ear wherein the organ is small tilted, displaced downward supernumerary tags preauricular sinuses and malformations of the external ear tissues.

Cutaneous Tags of the Ear, representative of abortive supernumerary ear tissue, are seen as fleshy growths projecting from the cheek just anterior to the tragus. They were found in 33 f 50,000 children bserved by W rner quoted by H y (AnnOtol 20 633, 1911) Costello a d Shepard (ArchOtol 29: 696, 1939) in a report of 4 cases, distinguished them from fibromas, which they have mistakenly been called and they are not nevus cell tumors. They are of various sizes, sometimes quite large and may contain cartilage continuous with that of the tragus or f the meatus.

Nevus cartilagineus was a name used by Miller and Miller (ADS 60 601 1949) who noted that they may occur anywhere along a line from the tragus t the angle of the mouth or on the neck along the sternomastoid muscle. One of their cases was cervical in location. Association with other branchiogenous facial defects was noted by Brander (ActaD-V 70 313 1939) Aural chondromas were described by Hennes (AfKinderh 9 436, 1888)

Unsightly they deserve correction for cosmetic reasons. Plastic surgical treatment was discussed by Co (NYSJM 39: 1936 1939)

Congenital Auricular Fistula occurs as a tract with its orifice marked by a shallow depression just a terior to the ascending limb f the helix abov the tragus. The depth is

variable and may extend even to communication with the middle ear or nasopharynx. The lesions are not rare. Irregular periods of infection and inflammation are usually the occasion for their discovery (Costello: ADS 60: 1016, 1949). The lesions may be unilateral or bilateral. The crux helicis or even the lobe may be the site of the orifice. Abnormalities were found in 1% of white children and in 5% of Negro children by Selkirk (AmJDisChild 49: 431 1935) who reported 172 cases of fistula, of which 23% were bilateral.

Four cases of "sinus preauricularis" were reported by Becker and Brunschwig (AmJ Surg 24: 1 4 1934) and 2 by Pasick (South MJ 38: 103, 1945). The affection was present in a man and his son and daughter (Montgomery SurgClinNoAm 2: 141 1931). A woman and 5 of her children showed the anomaly in the report of Fox (ArchOtol 35 431, 1942). The familial type seems to be due to a dominant autosomal gene of variable penetrance (Donald: AustralJD 1 253 1952).



Figs. 1548 and 1549.—Congenital fistulas of ear and of upper lip. (Becker: ADS 48 128, 1943.)

Figs. 1550 and 1551.—Secondary infection of congenital auricular fistulas. (Pastor and Erich AOtol 36 120 1942.)



Figs. 1552 and 1553.—Congenital fistulas, longitudinal and cross sections. (Drs. Becker Pastor and Erich.)

Cyst formation occurs and dermoid cysts are found here sometimes (Pastore and Erich AOtol 36 1?0 194.) The branchial cleft origin was postulated by Heusinger (AfPathAnat 29: 358, 1864).

Fistula of the Dorsum of the Nose.—A pinpoint sinus, from which yellowish matter hair blood and watery fluid are from time to time discharged or squeezed characterizes dermoid lesions of the dorsum of the nose. The sac is commonly of collar-button shape extending through the nasal bones. These rare lesions are usually unilocular (Rosedale OhioMJ 38: 132, 1942).

Four groups of cases were distinguished by Longo (ArchOtol 18: 753 1933) according to their location (1) those lying between the lower margin of the nasal bones and the tip of the nose; ( ) those on the bridge of the nose; (3) those near the tip; and (4) those at

the inner angle of the orbit in the nasofacial sulcus. Benjamins (ActaOto-Laryng 24 284 1936) attributed the lesions to burial of ectodermal rests during faulty development of the regio sulcus supranasalis. Infection is likely to complicate the lesions spontaneously or as a result of manipulation. There was hair in the penetrant fistula present since birth on the nose of a boy 4 years old, reported by Hagens (ArchOtol 23: 390 1933)

Curative surgery must be thorough and may be quite difficult (Brunner and Harned ArchOtol 36 86, 1942) although the cyst in the case of Costello et al. (ADS 60 1209 1949) did not extend under the cartilage as many of them do

Congenital Fistula of the Lower Lip may exist as a painless cosmetic defect sometimes associated with a deeply dimpled chin or with a dimple beside the anterior nasal spine (Lady: ADS 38: 151, 1938; Lady and Shirazy: InternatClin 3: 75 1938 familial, bibliography Gurney: WestJBOG 48: 753, 1940)



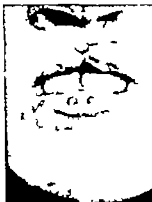
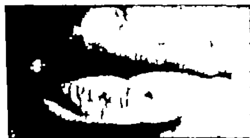


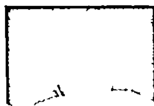


Fig. 1554.—Congenital preauricular fistula with scarring from repeated infections. (Drs. Pastor and Erich.)

Fig. 1555.—Congenital lip pits in a boy, 12 years old, who had also cleft palate and cleft lip. (Dr Sterling V Mead, Diseases of the mouth, The C. V Mosby Co.)

Fig. 1556.—Congenital fistula of dorsum of nose, showing injection of opaque medium and connection of sinus tract to cyst underlying nasal bones (Dr John F Bowser)





Figs. 1557 and 1558.—Congenital fistulas of lower lip, and roentgenogram of wires in fistulas. (*Lady and Shirazy InternatClin 3: 75, 1938.*)

Pits of the Lips.—Deep tracts on each side of the midline of the lower lip were described by Mason et al. (SGO 70: 18, 1940)

Fistulas of the Labial Commissures are symmetrically located in the angles of the mouth. The orifices are within the mucous surface of the labial commissures, and the canal, perhaps half a millimeter in diameter, extends laterally to a variable but shallow depth between the interlacing muscle fibers of the orbicularis oris. There occur in them mild, but annoying and sometimes stubborn, infections.

Treatment of Congenital Sinuses of all types is excision, which is sometimes hard to do. Inconsequential lesions may be neglected, but all cystic ones ought to be removed in view of their potentiality for serving as the point of origin of carcinoma. In delineating the course and extent of sinuses and fistulas and the ramifications of cysts, which are by no means always simple preoperative injection into the tract of methylene blue solution or roentgen

ologic study utilizing the injections of radiopaque substances, greatly clarifies the necessary surgical planning and work. It is highly inadvisable to attack these lesions without adequate preliminary study especially on the part of a dermatologist who may quickly find himself surgically beyond his depth.

The Dilated Pore.—A discrete enlarged pore is seen not infrequently its location usually on the face giving the lesion cosmetic significance. The

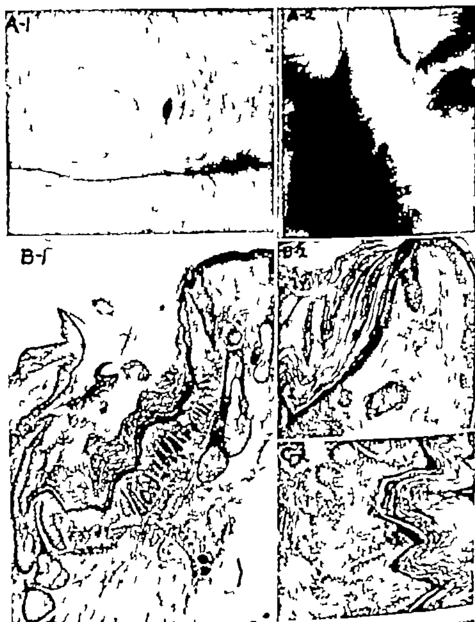


Fig 1869.—The dilated pore. B-1 a photomicrograph of the upper lip lesion seen in A 1 shows a- trophy of ostial epithelium, hyperplasia of follicular wall, lanugo hairs in wall and relation of lesion to sebaceous gland and hair follicle. B-2 and C 2, photomicrographs of the nose lesion seen in [illegible] A 2, show atrophic ostial epithelium and proliferating epithelium of the floor of dilated follicle (Winer JID 23 181 1954.)

face is not the sole possible site for lesions may be found in the areas subject to acne and comedo formation and they are not always solitary. The history is as a rule that the patient has from time to time over a period of years expressed the comedolike content but the cavity has gradually enlarged and the material in it has become more and more difficult to evacuate. Histologic studies of a number of such lesions by Winer (JID 23 181 1954) dis-

closed what he interpreted as trichoepitheliomatous structure the epidermis at the ostium was atrophic, but deeper in the follicle it became hypertrophic, developing numerous epidermal pegs, proliferations and papillomatous processes. The hair follicle not the sebaceous was involved for fat gland tissue if it were formerly present, was absent, possibly having been replaced by the epithelial overgrowth which extended laterally beneath the orifice to a distance of a millimeter or more. Thus excision must be wide lest there be left behind some of the acquired, benign epithelioma. Treatment since its aim is cosmetic is a challenging problem. Winer recommended excision.

Cysts are lesions which particularly justify the statement of Bland-Sutton "Many tumors become manifest by the accumulation of the products of their own activity" The following are of especial dermatologic interest see also





Fig 1560.—Wens, and, fortuitously alopecia areata. (Dr J P Guequierre.)
Fig. 1561.—Sebocystomatosis of scrotum.



Fig 1562.
Comedo-milium



Fig. 1563—Milia.
(Dr Stuart W y)



Fig. 1564
Synovial lesion.

capillary varix (blood cyst) epidermolysis bullosa epithelioma adenoides cysticum hydrocystoma hygroma (lymph cyst); lymphangioma mucus retention cyst ranula syringocystadenoma thyroglossal cyst venous varix.

Milia are small, white, dense discrete noninflammatory cystic papules due to retention beneath the epidermis of material from occluded normal or rudimentary sebaceous glands. Often associated with comedones milia differ in that the corneum covers the sebaceous content so that this sebaceous material is white being not oxidized black like the exposed surface of a black head. Sometimes milia are numerous and comedones are absent. The sites of predilection are the forehead, malar zygomatic and eyelid areas. Any area where there are sebaceous glands may be affected. Milia of the lip are sometimes seen in Fordyce's disease

The miliary cysts are a common neonatal disorder of the cheeks chin, nasolabial region forehead and upper trunk (Gordon: AD'sChild 24: 286, 1949)

Milia and comedones often appear at the edges of a zone treated with large doses of x ray therapy such as a basal cell carcinoma, as a result of deformity of sebaceous glands by roentgen energy (Ronchese ADS 61: 498, 1950) They occur at times on the palatal raphe of an infant Milia may appear following separation of the epidermis and replacement thereof such as occurs in many conditions, including epidermolysis bullosa, pemphigus (Ormsby: ADS 28 246, 1933) and even therapeutic sandpapering Remarkable involvement of the backs of the hands followed dermatitis venenata in the case of Tolman (ADS 60 9?7 1949) who quoted the instance due to sunburn reported by Dietel (DWchr 98: 1037 1934) Horny epidermal cysts may follow the application of coal tar (Chmel ActaDV 29: 476, 1949); see also Comedo, Acne, Chloracne.

An unusual and extensive case of milia was reported in a girl by Ronchese (ADS 60 935 1949) a case resembling ulerythema ophryogenes (q.v.)

The lesions on rare occasions undergo calcification (see p 1138 also Costello: ADS 56 536 1947)



Figs. 1565 and 1566—Multiple epidermal cysts and erythema affecting cheek of 11 year-old girl with keratosis pilaris (Ronchese: ADS 60: 935 1949) The same disease was described as "keratosis pilaris atrophicans faciei of Brocq by Fisher and Wolf (ADS 29 111 1934) who presented 3 cases in girls. The symmetric lesions are studded with granular milia set upon diffuse erythema, and the association with keratosis pilaris is usual. [illegible] cured [illegible] a boy with x ray therapy and Premarin tablets. Compare Ulerythema ophryogenes

Milia are persistent but harmless. Picking at them with dirty instruments may lead to infection or scar The presence of many milia usually signifies that the patient ingests a good deal of milk and ice cream.

Sebaceous Cysts are smooth, globular pea to orange-size or larger cutaneous or subcutaneous tumors which arise from the sebaceous glands and are usually located on the face neck back or genitalia. The tumors may be solitary or multiple and show variability in color and consistency They may be whitish pinkish or purplish in hue and soft, doughy elastic or firm to the touch They may be inflamed or quiescent. They commonly occur in middle age and are rare in the developmental period of life The lesions may be rounded, flattened, or irregularly globular The glandular orifice persists near the center In it one may find a blackened waxy comedo-like plug, or from it may be discharged a stinking secretion. The surface of the tumor is usually smooth and may become shiny and hairless because of the atrophy of the follicles which results from expansion under the skin. The tumors may reach enormous size and cause repulsive deformity

Cutaneous horns occasionally develop from the small, patulous cysts, and these generally have the histologic structure of calcifying epithelioma (q v)

A milium is a minute cyst occurring in a sebaceous follicle as a hard, white subepidermal object which can be picked out through a tiny slit made in the overlying tissue. Lesions intergradient between comedones, milia and sebaceous cysts are commonplace. The larger the accumulation of sebum which has a rancid butter odor the more obscure becomes the orifice representative of the sebaceous follicular mouth. While diagnosis ought to be easy it is often erroneous when the clinical opinion is checked histologically (Gross: J 152 813 1953)

Chalazions analogues of sebaceous cysts, are small tumors which develop on the eyelids from the meibomian glands

A sebaceous cyst is by definition a cystic alteration of a sebaceous gland a wen is presumaby a retention cyst, and an atheroma and a cholesteatoma are wenlike, filled with cholesterol crystals and similarly lined with stratified squamous epithelium.

Histologically the cyst consists of encapsulated masses of epithelial cells, in various stages of degeneration and disintegration and cholesterin crystals. The capsule, composed of fibrous connective tissue is lined with stratified squamous epithelium. It and its lining may be infiltrated with lipid matter Inflammation involving these cysts and their capsules may be reaction to either lipid or bacteria or both. Abandonment of the name ' sebaceous cyst was recommended by Stout (JMoMA 46 261 1949) who preferred to use the term epidermoid cyst.

Squamous carcinoma not infrequently develops in an epidermoid cyst sebaceous or atheromatous. Some 43 cases of this sort were collected by Ricker and Schwalb (Die Geschwülste der Hautdruesen, Berlin 1914) 3 by Seff and Berkowitz (SGO 23 469 1916) 12 by Caylor (AnnSurg 82 164 1925) 11 by Bishop (AnnSurg 93 109 1931) 3 by Collins (CanadMAJ 35 370 1936) who considered all cases to be precancerous, and 14 by Peden (AnnSurg 128: 1136 1948)

All should be removed, and all should be examined microscopically (Erich AmJSurg 50 672, 1940) Removal of sebaceous cysts is surgical, and many methods have been advocated. Because of the usual presence of an epithelial connection with the epidermis of the surface, which must be removed, an elliptical incision is generally made, sacrificing the skin which contains the orifice. The incision follows the margin of the lesion, which is attached more or less inextricably to the skin immediately overlying it. Removal of the cyst by dissection is facilitated by injecting the anesthetic fluid with hyaluronidase added to it intradermally continuing until it has swelled the entire capsule and has established a line of cleavage (Knight MinnM 22 105, 1939) Then the tumor is peeled out from its stringy slimy capsule. If excision is not complete, the cyst will recur Subcuticular sutures with 000 catgut can be used to avoid holes in the skin and to obtain minimal scarring Closure must be neat if good cosmetic results are to be obtained, and the dead space must be eliminated by means of a firm compression bandage during the first day or two. Scarring caused by stitches can be eliminated in suitable cases by removing them at the end of 24 hours and holding the wound together with Scotch cellophane tape.

When a sebaceous cyst has undergone abscess formation, it should be widely opened. Débridement must be carefully performed in the attempt to remove all of the lining Swabbing with liquid phenol followed by alcohol may make this easier The open wound is dressed with an antibacterial, such as tetracycline ointment. Closure may be allowed to take place spontaneously or the edges may be sutured later

The lesions can be eradicated by means of caustics, such as phenol or a bit of solid silver nitrate, put into the sac after the contents have been squeezed out through a narrow incision (Shaw: SoCarolMAJ 35: 90 1939) Feldman (ADS 34: 492, 1936) recommended

injection of the cyst with alcohol and expression of the content through a small opening, in the hope of minimizing the scar. Way (1939) told me he made a nick straight in with a pointed blade large enough to enable him to insert an applicator. He expressed the content, wiped out the cavity with liquid phenol, cleansed the skin with alcohol, and later expressed the necrotic sac or pulled it out with forceps. Fishman (USNMB 48: 917 1948) used a similar method, but after expressing the content he inserted a bit of solid silver nitrate and the next day extracted the lining. Dunna (NOrIMSJ 98: 6, 1945) inserted a sharp needle vertically, just entering the cavity, and applied monopolar diathermy via this electrode, sufficient to induce a slough of about one-fourth the diameter of the cyst. In healing, the cyst wall would contract and become level with the epidermis (see J 135: 320, 194). This electrosurgical technic was investigated histologically by Robbins and Pesky (ADS 62: 411 1950) whose coagulation of the skin was in a radius never greater than 1.5 mm. about the needle; a week later they removed the entire content and the sac. A method using the injection of a sclerosing solution was described by Kelley (NYSJM 60: 679 1950)

Steatomas (Wens) are smooth, globular pea to orange-size or larger subcutaneous tumors, which arise probably from hair anlagen. They are usually located on the scalp. A wen is presumably a retention cyst (Love and Montgomery ADS 47: 185 1943). Atheromas and cholesteatomas are wenlike, being filled with cholesterol crystals and similarly lined with stratified squamous epithelium. Paget (*Lectures on Surgical Pathology* London, 1853) believed that a wen is a dermoid cyst, for if it is cut open its lining assumes the character of skin. It does not granulate as a sebaceous cyst does.

The tumors may be solitary or multiple. They may be inflamed or quiescent. They commonly occur in middle age. Women are affected more frequently than men. They may be inherited as a dominant, sex linked to the female. Wens may disappear spontaneously if suppuration should destroy the lining membrane. They may be the site of chronic inflammation. Carcinoma may begin in them (see sebaceous cysts). They should be removed.

Excision of a wen is usually simple, for there is no duct connecting it with the epidermis of the surface and its lining membrane is tougher than that of the sebaceous cyst. After obtaining local anesthesia, and without shaving the scalp, a straight cut is made over the center of the lesion long enough to allow it to be expressed through the hole. Blunt dissection separates the membrane from the surrounding tissues, and the entirety of the lesion is popped out through the incision. This is closed by a stitch or two, and if the lesion was of moderate size no dressing is required. Finch (BMJ 1: 462, 1938) transfixed the base with a narrow blade and cut through the wall to the surface. He expressed the content and seized the wall on each side with a hemostat; by twisting this and clipping the adhesions he found it simple to remove the entirety of the sac. Even if the lesion is inflamed and its lining membrane ruptured, the entirety of its epithelium can generally be got out relatively easily.

Sebocystomatosis (Hereditary Sebaceous Cysts, Steatocystoma Multiplex) is an abnormality generally familial (Ingram and Oldfield BMJ 1: 960, 1937) in which a considerable number of atheromas are distributed over the body. The lesions are simple cysts, whitish, doughy and asymptomatic though disfiguring. The content is odorless, usually unoxidized and possesses chemical properties intergradient between those of blood lipid and depot fat (Lynch and Fisher JID 8: 65 1947). They may be limited in distribution to the scrotum, which then presents a curious appearance studded with white nodules (Ronchese ADS 49: 12 1944). Calcification of the content may take place (Dragoulides BsocfrançD 2: 294 1937). If patience suffices, the lesions can be removed. Since the onset is about the time of puberty as a rule, one would like to try the prolonged administration of estrogenic substances, which are helpful in acne (q v) and in chloracne.

Mount (ADS 36: 31 1937) attributed the first description of the condition to Bosellini (AfDuS 45: 81 1898). Pringle (BJD 11: 381 1899) gave a good account of it. Pollitzer (JCutGUDis 9: 281 1891) described a case with dermoid cysts so numerous that they simulated xanthomatosis. Ormsby and Finnerud (ADS 22: 822, 1930) published a review. Monro (JGenetics 3

61 1937) thought seboeystomatosis due to a single dominant character the gene being either heterozygous or homozygous; the cysts, he thought, are probably new formations, not sebaceous glands or sequelae of acne.

See Weber (BMJ 2: 204, 1937), 2 brothers Sachs (ADS 38: 877 1938) 10 cases in 3 generations Edit (BMJ 2: 358, 1938) inheritance; Puente and Cordiviola (RevArgentD 23: 330, 1939) case and review; Noojin and Reynolds (ADS 57 1013, 1948), 12 cases in 3 generations Lewis (BJD 60 264, 1948) vulvar case Anderson (BJD 62 218, 1950) 2 cases, review Lewis (ADS 68: 320 1953) girl, onset at ag 11 with hypercholesteremia.

Apocrine Cysts of the Scalp—These lesions, uncommon ones, resemble wens but are softer for they contain fluid not wax. The purplish color may show through the overlying skin. On undertaking excision one finds the sac thin walled but ordinarily easy to separate from the encapsulating connective tissue. The cyst is black when removed, but, after it has been in formaldehyde for a few hours, the color bleaches so that the tumor comes to resemble a thin, flabby bladder filled with urine The wall is lined by a layer of columnar epithelium with dark round nuclei and eosinophilic cytoplasm, and this lies on a layer of flattened cells, so that the apocrine origin is apparent. Tiny sessile or pedunculated glomera of lining cells project here and there into the lumen. One may imagine that if these papillations were profuse and proliferative the resultant lesion would be a cylindromatous syringoma. Diagnosis may be made before excision, by aspiration the fluid content is black, colored evidently with lipofuscin, and when it is centrifugated and stained one sees the round, dark nuclei and epithelial cells that have exfoliated from the lining These tumors are benign. They should be excised.

Dermoid Cysts.—The lining of these cysts is stratified squamous epithelium, and accessory skin structures are present, including sebaceous gland hairs, sometimes coil glands and even teeth. About such cysts there may often be found rudimentary tissues and caricatured organoid structures of nervous, muscular or other systems; such examples are true teratomas. Warthin taught that practically all dermoid cysts would reveal teratoid tissues if serially sectioned and carefully studied. Sutton (Dermoids, London 1889 be Lancet 2 1120, 1889) stated that dermoid cysts occur along the lines of coalescence of the embryologic clefts and of the opposite halves of the body wall. New and Erich (SGO 65: 48 1937) reviewed 103 cases involving the head and neck, grouping them thus: (1) those about the eyes, in the orbits and along the naso-optic groove; (2) those about the nose associated with the suture lines resulting from the intrusion of the frontonasal plate; (3) those in the floor of the mouth from the upper branchial arches; and (4) a miscellaneous group most f which were midventral or middorsal. Dermoid cysts may occur almost anywhere in the body Moir (BMJ 1: 463, 1936) recorded 2 of the mediastinum 1 was treated by excision and the other was marsupialized. Ovarian and testicular dermoid cysts are commonplace The cholest rol of the sebaceous contents is likely to crystallize within such tumors and one class f them, characterized by chronicity and slow growth has been designated cholesteatoma ; these comprise a class of surgically curable intracranial tumors (Love and Kernohan J 107 1876, 1936)

Dermoid cysts constitute a class of subcutaneous cysts. As seen by the dermatologist, they re generally located about the head or neck (see Congenital dermal si uses) and are diagnosed as dermoid by histologic study afte removal. They are to be e cised, and the danger that squamous carcinoma may originate within them makes this urgently desirable if the patient permits (Kent: JAMA 83: 377 1936)

See Montgomery and Morest (JAMA 31 486, 1934) mesenteric case; Shore (AnnSurg 103 305, 1936) 4 cases, floor of mouth; Nürnberger (FrankfZtschrPath 52 448, 1938) 178 cysts, 121 epidermoid, 40 dermoid, 17 traumatic, cancer in 7; Lereboullet et al. (Sang 12 883, 1938), in spleen; Hadley (BritJSurg 27: 140 1939), floor of mouth; Quade and Craig (PRAIMC 14 489 1939) colla button lesions of scalp, | volving diploe, with bony defects demonstrable by x ray Leidler et al. (AmJClinPath 21: 852, 1951) intracranial Whalley (BJD 64: 194, 1952) large scalp tumor

Traumatic Epithelial Cysts of the Skin.—It seems to be possible for a bit of epidermis to become traumatically displaced to a position beneath the surface There its continuing to proliferate results in the development of a subcutaneous or intradermal, hard, round, cystic tumor lined with stratified squamous epithelium, filled with horny débris and surrounded by a capsule of centrifugally displaced fibrous tissue. When epithelium proliferates in the absence of a free surface to grow upon, concentric corpuscles are formed; such were produced experimentally in Triturus by Kent (AnatRec 73: 275 1939)

White (JPathBact 14: 450 1910) injected oleic acid into experimental animals and obtained sterile abscesses which acquired epithelial linings. Ledingham (JPathBact 34: 123, 1931) confirmed these findings with the injection of various irritant substances and believed that the source of the epithelium is chance contact of the lesion with epidermis or accessory structure. Osteomyelitic cavities acquire a partial or complete epithelial lining by the growth into sinuses of cutaneous epithelium (Brunschwig: SGO 53: 720, 1931) Erdheim (AfPath 283 854, 1932) observed similar lining of the diploic cavities in tuberculosis of the calvarium. Gingival epithelium may grow along the wall of a sinus so as to form a dentigerous cyst (Grawitz, quoted by Morehead and Dewey: Pathology of the Mouth, Saunders 1925, p. 439) Cysts developed at the sites of insulin injections in a diabetic seen by Cornbleet and Reifer (ADS 43: 1067 1941)

In typical implantation cysts, the lesion is subcutaneous and of pinhead- to cherry size. The location is usually on the volar skin of the hand or finger Slow enlargement and slight tenderness are the rule. King (BritJSurg 21 29 1933) reporting 5 cases, called attention to the latent period usually intervening between the injury and the clinical appearance of the cyst, which may



Fig 1167 —Barbe pilonidal sinus the typical interdigital lesion, and photomicrographs showing (above) a cyst formed in the dermis at the end of a pseudofollicle, and (below) higher magnification of the cyst wall and varicolored hair within it. (Joseph [illegible] ADS 70 616, 1954.)

progress rapidly thereafter He *thought* the lining probably does not arise by implantation of skin. Trauma is not necessarily the essential element of such lesions for epithelium continually proliferates and tends to grow along any surface favorable to its cultivation. Wien and Caro (J 107 197 1934) reported 3 instances. Their review of the literature showed that these benign tumors have long been recognized for Wörz (BeitrklinChir 18 733 1897) studied a series of 55 cases, though in only 24 was there a clear history of trauma

One must differentiate metastatic tumor synovial lesion, fibroma xanthoma, ganglion, sebaceous cyst, atheroma and dermoid cyst.

To cure excision must be complete

Cysts of the Terminal Phalanges, following trauma to the distal portion of the fingers, were studied by Bissell and Brunschwig (J 109: 1702, 1937); the lesion are pre-

gressive, gradual, diffuse swellings, suggestive of chondroma on x ray examination, with inflammatory symptoms wanting On peeling away the epidermal lining of a cyst, a simple matter, they said, the cavity heals by becoming filled with cancellous bo e. See Yachnis and Summerill (J 116: 1216 1941); Becker (Chirurg 13: 275 1941)

See Blond (ArKlinChir 120 495, 1922), Behrens (ArPathAnat 280: 148, 1931); Strauss (UCutRev 39: 389 1934) case Mason (BDO 44: 126 1931), traumatic origin Cogswell and Goodale (JLabClinM 25 576, 1940) 37 cases Dolce and Clark (NYSJM 44: 2168, 1944) 4 palmar lesions

Hair Cysts.—Occurring generally in the hand of a barber this curious lesion has been described as a hair bearing sinus (Ewing Lancet 1 427 1947) or a form of pilonidal cyst due not to malformation but rather to granulomatous reaction to buried hair (Patey and Scarff: Lancet 2 13 1948) Such tumors are found in the skin of the interdigital web resembling im plantation cysts, from which they differ in becoming inflamed repeatedly from them hairs are occasionally extruded and extracted. A sinus tract ex tends into the interior of the nodule, which is lined with epithelium. Excision is required.

It is possible that lesions called pilonidal cysts are often in reality of this nature (Edit: J 138: 434, 1948) Four cases, all in barbers were reported by King (AustralNZealJSurg 19 29 1949) The remarkabl feature in 1 I saw was the evidence of growth of the hair suggesting that if it did in fact result from the embedding of hair into the skin by way of pore the hair shaft, although separated from its original root and follicle, manifested the ability to grow when it had incited as a foreign body the development of an epidermal sac. An axillary lesion of this type was seen by Aird (BMJ 1 902, 1952), and a suprapubic case by MacLeod (BMJ 1: 710, 1953) The name trichofolliculoma" was given by Miescher (Dermatologica 89 193, 1944) in describing a small nodule on the cheek from which hair was extracted; histologically he found a huge follicular orifice with many lanugo ha rs. Perhaps this was a hai cyst.

See Hueston (AustralNZealJSurg 21: 224, 1952) case, barber; Downing (J 148: 1301 1952) case, barber and review; Stable (AustralJDerm 1 289, 1952) case, hairdresser; Waterman and Olivetti (ADS 66 466 1952) case; Warin (IndustMAS 12 111, 1953) 3 cases, barbers Currie et al. (BritJSurg 41 278, 1953) lesions found in 10 of 77 male hai dressers in 18 barbershops, none in 61 female hairdressers; Joseph and Gifford (ADS 70: 616, 1954) occupational disease among barbers, 16 of 118 barbers had lesions, 1 of them with 6 lesions in 4 interspaces.

Synovial Lesions of the Skin.—Cystic lesions occur beneath the skin in the vicinity of joints, particularly on the dorsal aspect of the interphalangeal metacarpophalangeal and metatarsophalangeal articulations. The surface is usually smooth and shiny The lesions contain ropy clear yellowish fluid. If opened, they refill. Pain may result from internal pressure.

The apparently synovial origin of the cyst, it connection with the capsule of the underlying rticulation and its independence of the dermis and epidermis were demonstrated by MacKee and Andrews (ADS 4: 168, 1921; 5 561 1922) Savatard (ADS 9: 441, 1924) described a series of cases with histologic studies and suggested that they may be periarticula fibromas, cystic because of myxoid degeneration. The relation to ganglion is suggestive: like ganglion, in which opaque injection showed no connection with joint cavities (Halley: SouthMJ 25 259 1932), I have not found these lesions continuous with articular spaces. The hypothesis that they arise by escape of synovial fluid (Ellassow and Frank ADS 46 691 1942) is not attractive to me.

The lesions may be dissected out sharp but are likely to recur They are generally radiosensitive and Sutton (J 67 387 1916) reported good results with radium. In giving x ray therapy an ample margin should be allowed in order to produce atrophy of marginal tissues, from which recurrence may otherwise take place. The dose suggested by Woodburne (ADS 56 407 1947) is 500 r with 1 mm. Al filtration at intervals of a week or 2 until some 1,500 to 2,000 r have been given; less is seldom curative, and scarring from this dose is not consequential. Solid carbon dioxide can be used so as to cure and was preferred by Anderson, he told me. King (AustralNZealJSurg 21 121 1951) calling the lesions mucous cysts, recommended plastic surgery which is seldom necessary A treatment sometimes applicable consists in obtaining local anesthesia, then applying the actual cautery to the top half of the lesion in such a fashion as to destroy and remove this portion. After cauterizing the base a bland ointment dressing is used the wound heals without event, and the scar is entirely acceptable.



Fig. 1568.—Synovial lesion affecting proximal interphalangeal joint region





Fig. 1569.—Cyst in skin of fifth finger (see Figs. 1571 and 1572)
Fig. 1570.—Synovial lesion of skin. (Drs. George Miller Mackee and George C. Andrews.)



Figs. 1571 and 1572.—The structure of cyst shown in Fig. 1569, and high magnification suggesting its origin in synovial endothelium. (Col. W. F. Harvey.)

See Hyde (Diseases of the Skin, Philadelphia, 1883) Lingenfelder (JCutD 31 647, 1913) warty lesion; Ormsby (JCutD 31 942, 1913) 4 cases; Montgomery and Culver (ADS 8: 319 1923) x-ray therapy; King (BritJSurg 18: 594, 1931) synovial sheath tumors, King (AustralNZealJSurg 1: 367 1932) ganglion due to spindle-cell proliferation; Gross (BGO 65 289, 1937) etiology in myxomatous degeneration of the cutis Fehr (BeitrklinChir 165: 88, 1937), synovioma of knee a slow-growing sarcoma requiring amputation, Berger (AmJCanc 34: 501 1938) synovial sarcoma, 5 cases and review; Brunschwig (Surg 5 101, 1939) synovial tumors of hands and feet; Jacox and Freedman (Radiol 36 698, 1941) 7 cases, x ray therapy; Wright (BritJSurg 38 257 1951) benign giant cell synovioma, 85 cases, 69 of hand.





Fig. 1573.—Horn produced by calcifying epithelioma
Fig. 1574.—Calcifying epithelioma of forehead.

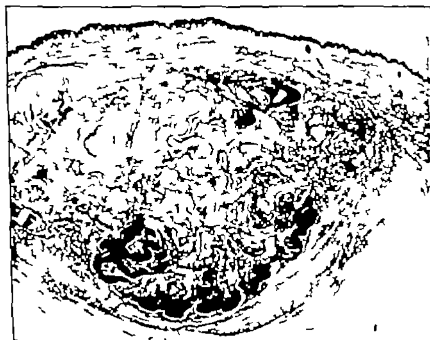


Fig. 1575.—Calcifying epithelioma; nodule from young woman forearm, showing topography calcification of bands of stratified epithelium, stroma, and encapsulation. (Sutton and Sutton ADS 31: 46, 1935.)

CALCIFYING EPITHELIOMA

Symptoms.—Calcifying epithelioma (Malherbe's tumor) is a slow growing firm or hard, sharply encapsulated new growth. It occurs on the head, arms, forearms and back, in order of frequency in persons who may be young or in early adult life The shape is basically spheroidally rounded. The size

is from 1 to 3 or even 9 cm. in diameter The location is within the dermis, fixed to the skin above and freely movable over the deeper tissues. It may ulcerate crust, and build up a hornlike mass of coherent débris (Sutton and Sutton ADS 31 48 1935)

Pathology.—Bands of stratified squamous epithelium are set in a dense fibrotic stroma remarkable for the giant cells in its structure. Some of the epithelium is living and proliferating some is decadent or dead and serves as a foreign body substance rich in lipids. Cholesterol clefts are commonly found. The stroma is to be interpreted as foreign body reaction. Ossification often occurs (Highman and Ogden APath 37 169 1944) The gross section has a gritty granular surface.

Etiology.—The lesions may develop from wens or cystic tumors. They are usually clinically mistaken for cysts. They might be explained by discontinuity resulting from trauma or inflammation, in the wall of a cyst with an epidermal lining allowing foreign body reaction on the part of the mesodermal tissues to take place, while epithelium which previously lined the cyst simply continued to proliferate.

Treatment.—These tumors behave as benign neoplasms of local growth, amenable to simple excision.

See Chenantais (Thèse de Paris 1881 abs J CutD 1: 31 1883) Walkhoff (Festschr Rindfleisch, Leipzig, 1907 p. 222) case, bibliography Kaufmann (Lehrbuch d. spez path Anat., Reimer, 1911, v 2, p 1321), Stramberg (AfpathAnat 203: 131, 1911) 6 cases Linden (Ztsch Krebsfor 12: 506, 1912 13) case, quoted Wilkens' description in 1858) Nicholson (JPathBact 21 287 1916-17) bone formation Dubreuilh and Cazenave (DermatD 6: 306, 1921) histology Flarer (UCutRev 25 284 1931) 2 cases, arm, in females, bibliography Ch'in Kuang yu (AmJPath 9 407 1933) 8 cases, review Yamasaki (JapJD&U 33 812, 1933) case; Yoshikawa (Hihu-to-Hitunyo 5 10 1937) 2 cases, review of 26 in Japanese literature Forster and Levy (RevChir 57: 708, 1938) case with ossification, cheek Favre et al. (AmédDerf 42 73 1939) 7 cases in infants Fischer (DWchn 111 1602, 1940) Highman and Ogden (APath 37 169 1944) 12 cases, 6 with bone formation King (AmJPath 23 23, 1947) 6 cases of "mummified epidermal cysts Setala (abs YBD 1949, p 261) 27 cases, half from head, 7 with bone formation Lever and Griesemer (ADS 59: 506, 1949) 16 cases, review Temple (BMJ 1 920, 1951) 11 cases Tilden (ADS 66 728, 1952) 13 cases; Castiglione and Rominger (ADS 70 590 1954) 2 cases, occipital in an old woman and parotid in young one.

SEBORRHEIC KERATOSIS

Seborrheic Keratoses (Acanthotic Nevi Senile Warts) begin as small, round warty brownish, sharply circumscribed thickenings of the epidermis. Persons beyond middle age are usually the ones involved. While the growths may occur anywhere on the skin their site of predilection is the trunk, contrasting with the senile keratosis and its predilection for exposed surfaces, for sunshine has nothing to do with their causation. When fully developed they are flat topped papules or tumors, oval in outline brownish or blackish in color sharply circumscribed perhaps pedunculated and vegetative but usually sessile sometimes verrucoid, and covered with an unctuous scale When the scale is carefully removed its under surface may present numerous tiny projections which formerly extended into the gaping mouths of follicle-like epithelial corrugations. The tumors seem never to disappear spontaneously and may persist indefinitely without change They may be solitary few or many Only very rarely does the epithelium of which they are composed become proliferative and carcinomatous. The change when it occurs, involves first a part of the lesion, and the process spreads. The lesion becomes vegetative crusted and malodorous the microscope reveals a papillomatous, medullary squamous carcinoma. The tendency to malignant change however is slight. Occasionally they are quite itchy especially when numerous and located under pendulous breasts.

Seborrheic keratoses may be numerous disseminated fairly symmetrically over the trunk and abdomen, sometimes the arms or forearms. I have seen them arranged in vertical streaks following the striae distensae over a woman s belly They are not to be confused with the keratinizing series of epi-

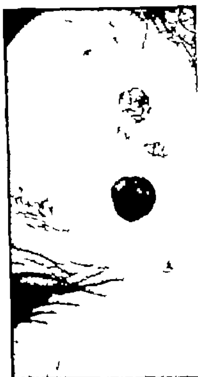




Fig. 1576.—Seborrheic keratoses on forehead.
Fig. 1577.—Multiple seborrheic keratoses.





Fig. 1578.—Seborrheic keratoses of vegetative type. (Dr. A. J. Markley.)
Fig. 1579.—A tremendous seborrheic keratosis of an old man clavicular region.

dermal new growths which comprise the senile keratoses and early squamous carcinomas Compare Verruca plana juvenilis; Papillomatosis Epidermodysplasia verruciformis Cutaneous tags of the neck.

Squamous Cell Keratosis.—A small minority of lesions of the clinical appearance and microscopic architecture of acanthotic nevus are composed of cells which have the staining qualities of keratinizing stratum Malpighii and which retain their intercellular spines in these are generally to be found



Fig. 1148.—Seborrheic keratoses A, typical lesions on the back. B, [illegible] type of structure with [illegible] papillae [illegible]

whorls of keratinizing epithelium simulating the pearl formation of squamous carcinoma. These are essentially similar to the ordinary seborrheic keratosis although they may represent vegetative squamous cell neoplasia of high coherence and l w growth rate

Cutaneous Tags of the Neck.—Tiny fibrotic outgrowths resembling molluscum fibrosum are frequently observed about the neck especially the anterolateral a pects, of women more often than men (Templeton Alb 33

495 1936) These lesions seem to be verrucae planae or seborrheic keratoses. They are not apparently influenced by endocrine relationships. They are easy to destroy individually with a pointed cautery or an electrodesiccator

GRANULOMA SENILE.—Under this designation, Kreibich (quoted by Johnson and Harvey: ADS 21: 566 1930) described a rare lesion which resembles a malignant change in a senile wart, and which he thought should be differentiated from epithelioma and from granuloma pyogenicum. Johnson and Harvey reported a similar case a man of 71 years, whose tumor resembled a lobulated epulis and was located behind the lobule of the left ear It was a crusted, reddish nodule which had developed from a greasy keratosis. In such lesions as answered this description in my experience, the microscope has revealed a medullary type of carcinoma with squamous cells which do not form horny pearls If Johnson and Harvey's case was truly benign inflammation, it was probably granuloma pyogenicum or an acanthotic nevus.

Pathology of Seborrheic Keratosis.—The microscope reveals acanthosis, the thickened epithelial layer being papillomatous to a greater or lesser degree. The cells are ordinarily similar to those of basal cell epithelioma, being uniform, basophilic, fairly regular somewhat spindle-shaped, and palisaded along the dermo-epidermal junction, which is unbroken. Dermal papillae are elongated and their vessels dilated. When a seborrheic keratosis is excised and soaked in water a few hours, the papillomatous dermis is rendered apparent, for the greasy scale loosens and partially falls away The removal of the epidermis by application of the actual cautery followed by wiping with an alcohol sponge likewise reveals the structure, for long, denuded, dermal papillae then project from the surface Acanthotic epithelium degenerates externally to form the greasy external material which covers the tumor Among and between its cells are dendritic cells containing melanin granules. Some lesions contain much more pigment than others. See Becker (ADS 63 358 1951) whose essay is fully documented.

Diagnosis.—Senile keratoses and early epidermal carcinomas are distinguished by their harsh, horny scale. Melanotic nevi may closely simulate acanthotic nevus as a rule, true nevus has existed since early youth, while the keratosis is acquired at a later age

Prognosis.—The lesions are benign. It would seem that basal cell cancer pigmented basal cell cancer and perhaps, keratinizing carcinoma may occasionally originate in them, although this is rare They seem to behave as if they were autoinoculable

Treatment consists in destructive removal of the epithelial cells which comprise the tumors, which must be treated individually Any physicotherapeutic agent which blisters can be used I prefer the actual cautery Accurate separation of epithelium from dermis may be accomplished, and with gauze moistened with alcohol the heat loosened epithelium may be wiped away, leaving a denuded but relatively unharmed cutis, the hypertrophic papillae of which one burns flat. The wound heals in from 7 to 14 days, and little or no scar results. Radium or x-rays in unfiltered dosage for a superficial peeling effect will accomplish almost the same end. Solid carbon dioxide may be used. Trichloracetic acid was highly recommended by Montgomery and Culver (JCutD 30 523 1912)

See Sutton (J 60 1774, 1913) seborrheic keratoses of lips Sutton (J 64 403 1915) varieties of seborrheic keratoses, treatment; Eller and Ryan (ADS 22 1043, 1930) differentiation of senile and seborrheic keratoses; Montgomery (MinnM 18: 738, 1935), clinical and histologic differences between verruca and keratoma senile Montgomery (SurgClinNoAm 17 1249 1937) bibliography; Raff and Raff (PrensaMedArgent 26: 2311, 1939) fluorescence of precancerous lesions; Fox (APath 36 198, 1943) brown, rounded, polypoid, button-like, warty lesions with pigmentation Sachs (ADS 50 179 1940) histologic descriptions of types; Ra [illegible] and Obermayer (JID 14 283, 1950), improvement with vitamin A; Hall (ADS 62 382, 1950) podophyllin curative; Becker (ADS 63 358, 1951) structure of solid, reticulated and serrated types; Caro and Szymanski (MedClinNoAm 35 1 1951) clinical and histologic distinctions; Reiches (ADS 65 596, 1952) inheritance as dominant.

SUPERFICIAL AND EARLY EPITHELIAL NEOPLASMS OF THE SKIN AND MUCOSAE

Senile Keratosis.—These circumscribed, horny lesions are flat dry harsh and brownish occurring by predilection on parts exposed to sunlight. Collectively they comprise a series of superficial epidermal neoplasms composed

of keratinizing epithelium, like the neoplastic lesions of xeroderma pigmentosum and those provoked by carcinogenic agents such as tar dibenzanthracene and radiation. Intergradations exist between keratoses which peter out and drop off, keratoses which reach a certain stage of growth and grow no further keratoses which slowly progress until they infiltrate the



Fig. 1581.—Senile keratoses.



Fig. 1582.—Senile keratoses.





Fig. 1583.—Senile keratoses.
Fig. 1584.—Senile keratoses with progress into squamous carcinomas.

dermis and continue to grow as obvious carcinomas, and keratoses which progress speedily from the start into swiftly growing squamous carcinomas. Therefore and in view of the fact that no sound prediction can be made about any given lesion at the moment of one's examination of it, I group the lot as epidermal neoplasms. Their benignancy or malignancy is intimately associated

with the rate of growth and the cohesiveness of the neoplastic cells (Sutton ADS 37 737 1938; 46 1 1942) The observer's knowledge of malignancy depends on observations of a particular lesion over a period of time.

Senile keratoses are flat or verrucose. Sometimes they surmount a more or less narrow peduncle so as to resemble filiform warts. The scale produced by the proliferation of the epithelium of which they are composed is harsh and horny It may be of greater or lesser degrees of cohesiveness, so that in one lesion there heaps up a horn of translucent yellowish appearance tightly applied at its base and in another there scale off flakes in thin laminae The patient complains of a tender spot If it is hard to see it may be easier located by scraping the skin with the fingernail than by looking for it.



Fig. 1585.—Senile keratoses and squamous carcinoma, illustrating of the various stages of carcinoma t progresses A blue-eyed, 58-year-old Kansas farmer





Fig. 1586.—Keratoses and carcinomas, indicating relationship between them: all re blastomas, and each is individual in behavior and clinical significance.

Fig. 1587.—Early carcinoma (neoplastic leukoplakia) of the cornea, an analogue of senile keratosis.

If one picks off the scale, one tears through the thin epidermis so that bleeding occurs. While the majority of individual neoplastic lesions never progress into actively invasive carcinomas, some 20 to 25% of them do according to the guess of Montgomery (ADS 39 387 1939) Fast-growing keratoses are set on an inflamed base and are narrowly surrounded by a zone of hyperemia (Stryker JMoMA 30 15 1933) These are early carcinomas. Compare seborrheic keratosis (p 1176) and bibliography given therewith.

ETIOLOGY — Age is a factor although keratoses may develop in young adults. An important element is a peculiar quality of the skin, a quality which is usually inherited and characterized by harshness, dryness and a tendency to freckle. Persons with such skins generally have reddish hair whether light or dark in hue and are sensitive to sunlight. Such a skin, with keratoses, is

sometimes called "sailors skin" or "farmers skin." The lesions which appear *in radiation dermatitis, arsenical keratoses* or *experimentally induced* carcinogenesis are essentially identical.

There are reasons for believing that a keratosis is a colony of cells which are the progeny of a somatic mutant. The initial change is intracellular, inherited by daughter cells, and irreversible (Sutton, ADS 37 737 1938). The time interval of 30 to 100 days between the application of a carcinogen and the appearance of visible tumors is difficult to explain in pursuing the hypothesis that a mutation initiates a malignant colony of cells from one cell (Sutton, ADS 46 32 1942). Studies of tumor cell populations by Monte Carlo methods (Hoffman et al. Sci 122 465 1955) may be pertinent. Probability distributions for tumor growths beginning with 1 cell were determined for various intermitotic time intervals by means of the Los Alamos digital



Figs. 1588 and 1589.—Keratosis from helix. Lesion was scaly because a circumscribed portion of epidermis consisted of abnormal cells, sharply demarcated from normal ones, exceeding normal ones in rate of growth, and abnormally coherent as evidenced by coherent of corneum they have produced.



Figs. 1590 and 1591.—Senile keratosis, showing its carcinomatous, if superficial, structure. From same patient as shown in Fig. 1589. Also from helix.

computer. Single cells might generate, it was found, widely differing numbers of cells in fixed intervals of time, and a long time was required for a cell population to attain steady growth.

PATHOLOGY.—An early neoplastic keratosis is a small roughly circular anomaly of the epidermis. The area is slightly browner or pinker than normal and may or may not possess a palpable harsh scale. In this stage the microscope reveals epidermal changes which have been variously interpreted as "unrest" or carcinoma in situ, or as separation of the basal layer from the remainder of the epidermis. Beneath the abnormal epithelium there is a more or less intense infiltration of leukocytes. The scale is parakeratotic in the places in which it is derived from the "restless" epithelium. This atypical epithelium grows, spreading beneath, engulfing and permeating the normal epithelium of the epidermis and its appendages.

In some keratoses which scale off readily so-called separation of the basal layer is likely to be found. I believe that this is not down budding but that neoplastic epithelium is here proliferating spreading and warping beneath the normal layer In other keratoses which scale off readily the microscope shows atypical epithelial cells spreading through the epidermal layer in small groups or even singly evincing no tendency to cohere with one another They cause by their proliferation a thickening of the epidermis, a filling and bulging of its papillae an appearance of unrest and a form of keratinization which is irregular and in part parakeratotic. In this kind of keratosis the cells may be hydropic so that the lesion cannot be differentiated from Paget s disease or Bowen s disease It is abnormal keratinization by cells that are neoplastic which in the aggregate is by some observers called dyskeratosis. While some keratoses scale off readily and are composed of cells which have no great tendency to adhere to one another or to form thick layers or large aggregates, many keratoses are made up of epithelium which persistently remains multilayered. This coherent epithelium thickens forms comparatively dense horn proliferates and expands in area, with the result that it buckles and warps, and produces lesions which are clinically warty or hornlike. The continued mitotic proliferation of a precancerous keratosis, by warping and buckling of its layers, eventually leads to invasion of the dermis, where the cells proliferate freely without wastage by keratinization (Mottram AmJCanc 22 801 1934) and produce the intracutaneous lesions of slow or speedy rates of growth which are carcinomas of different degrees of malignancy Senile keratoses are intraepidermal carcinomas.

Senile keratoses and seborrheic keratoses are two distinct disease entities (Eller and Ryan; ADS 22: 1043 1930); A clinical differentiation is not always possible. Senile keratosis is distinctly a precancerous condition. While such lesions may exist for many years without undergoing malignant changes or may never undergo such a change if a change does occur the epithelioma is always of the prickle-cell type. Senile keratoses never occur on other than exposed portions of th body Seborrheic keratoses, especially those on covered parts of the body may undergo malignant changes, but if they do occur they are rare, and w have never seen such a case. Those involvi g exposed portions may give rise to epithelioma; when they undergo malignant change, the resulting epithelioma is of the basal cell type. In study of 31 cases of keratoma senilis, and 52 cases of verruca senilis, Hookey (ADS 23 946, 1931) co cluded that, Malignancy arising from keratoma senilis is usually of the squamous cell, rather than of the basal cell, type. The mechanism of the development of malignancy in these lesions is imilar to that seen in Bowen's disease namely a result f the dyskeratotic phenomena [whatever they may be]

Clarification of the distinctions between seborrheic keratoses (q v) and senile keratoses have been described by Freudenthal (AfDuS 152: 504, 1926 158: 539, 1929); Montgomery (SurgClinNoAm 17: 1.49, 1931); Bloch (CancRev 7: 65, 1932); Ormsby (NE gJM 224: 793 1941); Miescher (SchweizMWchr 73: 1072, 1943) and others; and they have given sound but static morphologic descriptions, but fo the most part have neglected the point of view of dynamic histogenesis.

Cytochemical studies of senile keratoses showing altered mechanism of keratinization and variation of nu lear size and staining were reported by Leuchenberger and Lund (CancRes 12: 276, 1952)

Treatment.—Men whose faces are affected should shave carefully to avoid nicking the lesions, for this might effect the implantation of atypical epithelium into the dermis, where it would grow into carcinoma. The patient should diminish his exposure to sunshine. A thin coating of zinc oxide ointment or Afil is helpful to persons occupationally unsheltered. Advanced keratoid lesions resist ointment therapy, which merely removes corneum while underlying cells continue to proliferate. These must be destroyed. One thorough freezing with solid carbon dioxide will do it. I find the microcautery efficient after obtaining local anesthesia with procaine the point at high heat is wiped quickly over the lesion, an application sufficient to blister off all epithelium. The wound heals in from 7 to 10 days, often without a scar If the operation is too shallow recurrence as intracutaneous carcinoma may be expected. Admirable results can be obtained by the use of x rays or radium using a dose which peels, perhaps 1000 r In growths which are al-



Fig 1592.—Early squamous carcinoma. Topography revealed by section traversing from normal on one side to normal on the other. "Keratosis" 4 mm. in diameter from bulk. Neoplastic cells have at 1 completely replaced normal ones so that epidermis here is composed of cancer cells only. Their abnormal keratinization accounts for scaliness. Zone 2 would be called "erythroplasia" if it occurred on mucous membrane. From 2 neoplastic epithelium 3 has proliferated and expanded three-dimensionally at the dermo-epidermal junction, so as to lie adjacent to superficial portions of follicles and glands 7. Neoplastic epithelium 3 folds as the layer of it expands. Sections of folds 3 are two-layered. Terminations 4 of sheet of neoplastic epithelium are definite. Shearing stress of growth at dermoepidermal junction produces apparent space 4, an artifact. Erroneously interpreted as a separation of basal layer, this is in fact replacement of basal layer by cancerous epithelium, which is spreading centrifugally. See Fig. 1593. See Sutton (ADS 46: 1, 1942)



Fig. 1593.—Head [illegible] of Fig. 1592. See Sutton (ADS 37: 737, 1938)



Fig. 1594.—Early carcinoma. Compare Fig. 1592 carefully. This is further advanced. Compare Fig. 896 where carcinoma tissue is more coherent.

ready intracutaneous and progressive treatment is that of carcinoma. Vitamin A 100 000 units per day by mouth for several months, sometimes is salutary believed Dublin and Hazen (ADS 57 178 1948)

Histogenesis of Squamous Carcinoma.—While superficially located growth of neoplastic cells is productive of keratosis, growth in the dermis results in carcinoma. Many early squamous carcinomas of the skin are minute warty



Fig 1593.—Early squamous carcinoma, clinically a warty keratosis. See discoid and sharply circumscribed replacement of epidermis and warping of expanding disk of neoplastic epithelium, which coheres in keratinization so as to produce a horn.



Fig. 1594.—Early squamous carcinoma, a keratosis from the finger of a physician who had long handled radium. Where replacement of the whole thickness of the epithelium has occurred keratinization of carcinomatous tissue formed a horny spicule, which has fallen away as in Fig. 1593. Invasion of the dermis is apparent, along with the formation of horny pearls by spherical cornification.

lesions or minute dome-shaped papules with a central horny spike. The central cornification is characteristic of the lesions, for it inevitably results from their manner of histogenesis. They begin in one or few cells of the epidermis, and these cells proliferate so as to supplant the whole thickness of epidermis at that site. That portion of the corneum which is derived from the altered cells is different from normal corneum. Swiftly growing the altered cells soon invade the dermis, and their growth there may be in coherent masses,



Fig. 1597.—Small squamous carcinoma from the ear of a physician 70 years old, who had blue eyes and white hai , as is common in cases of squamous carcinoma. Not multilayered epithelial surface expanding and folding into the dermis, forming wartlike, rapidly growing lesion. It began as a "scaly spot.



Fig. 1598.—Small squamous carcinoma. Abnormal, parakeratotic corneum overlies cancer cells, is derived from them, nd identifies the extent of total epidermal replacement by them. The large horny pearl shows internal cornification this pearl was actually [illegible] t bule, cut in this section as an island, but communicating with the surface



Fig. 1599.—Early squamous carcinoma from the nose of a woma 85 years ol . Wart-lik in clinical appearance this is histologically obvious carcinoma. W rts do not degenerate into carcinomas; little wartlik carcinomas grow i t big carcinomas

the central cells of which cornify and form horny pearls; or their growth may be in incoherent, isolated cells, narrow strands or small groups. Degeneration and keratinization of cells lacking coherence lead to the appearance of highly anaplastic growth, signifying a high degree of malignancy. Pearl formation is well developed in lesions composed of coherent cells. Mechanical consid



Fig. 1600—Early intraepithelial, squamous carcinoma. Not yet eroded or ulcerated, this is a tiny papule composed of proliferating cancer cells, which balloon the epithelium and must sooner or later break through into the dermis beneath.



Fig 1601.—Early squamous carcinoma; pinkish papule with central horny spicule from the f ce of an lderly farmer. Complet replacement of the central zone of the overlying epidermis has taken place, and the horny spike, composed of keratinized cancer cells, shows parakeratosi. Cancer cells freely in de the dermis in ones and twos nd small groups, keratinizing indi idually as w ll as in small pearls.

erations make it evident that proclivity for metastasis hence malignancy is greater in lesions with cells which do not stick together (Sutton ADS 37 737 1938; 46 1 1942 Coman: CancRes 4 625 1944; Sci 106 347 1947)

Carcinoma in Situ refers in histologic description to neoplastic altera tion of epithelium limited to epidermal location. Senile keratoses and many varieties of early carcinoma are of this nature. See also Basal cell carcinoma, superficial (p 1247) and intraepithelial (p. 1248)

Leukoplakia.—Mucosal surfaces are normally uniformly covered with epithelium translucent enough to permit the red color of underlying capillaries to show through evenly When a zone of epidermis is neoplastic and cohesive the epidermal covering at that place is thick and so obscures in a sharply marginated region the blood color beneath Neoplastic leukoplakia is neoplastic keratosis on a mucous membrane It is irregular in outline but always is sharply marginated The thicker it is, superficially set on the mucosa the less instant is its danger in general for thickness indicates cohesive-





Fig. 1602.—Leukoplakia of the tongue (Drs. Fordyce and MacKee.)

Fig. 1603—Neoplastic leukoplakia in the common sublingual location The sharp margins and wrinkled surface of the lesion in this inveterate cigarette smoker are typical (Thoma Oral Pathology Mosby 1960)





Fig. 1604.—Leukoplakia of the tongue (Dr George M. MacKee.)

Fig. 1605.—Leukoplakic superficial carcinoma (Dr Fred W Ximan)

ness of its cells and their lessened likelihood of invading Thin, flaky easily bleeding leukoplakia like the analogous keratosis senilis is dangerous it simply requires time to do harm. Erythroplakia is of this type

The most frequent sites for the patches are the dorsum and lateral sulci of the tongue the inner surfaces of the cheeks along the interdental line and the gingivae, particularly at the angle of the jaw The earliest manifestation may be localized irritation with increased sensitiveness to hot and irritating substances. Redness follows, frequently with accentuation of the papillae and

in the course of weeks or months the lesions become apparent to the eye as sharply defined, variously shaped, whitish or slate-colored plaques, which give rise to more or less stiffness and immobility of the affected parts, but seldom cause pain.

The course of the histogenetic development of neoplastic leukoplakia into frank squamous carcinoma is exactly as it is on the skin. With invasion of mesodermal tissue, there occur induration loss of flexibility fissuring and the development of palpable tumor; and prompt metastasis is typical of ulcerative carcinoma of mucous membranes. Lesions which heap up in contrast with those which burrow in, are less malignant.

Etiology.—The individual who is prone to develop neoplastic leukoplakia and carcinoma of the mouth is the poorly pigmented male, possibly auburn haired who is also predisposed to develop chronic, xerodermatous, actinic dermatitis with neoplastic keratoses. On the skins of these people, it is the sun which immediately instigates the changes to which predisposition exists. In the mouth, it is generally the tarry distillate of tobacco which performs the same service. Saliva washes away much of the tar but where saliva dries along the external line of contiguity of the upper and lower lips, *not essentially* at the mucocutaneous junction, as has so often erroneously been asserted, the tarry substance incites epithelial abnormality along much or all of the extent of the lip The lower lip is affected principally for it is the one which is exposed to the sun as well as to the chemicals.

The causes of neoplastic leukoplakia are the causes of keratosis senilis, excepting sunlight Mere mechanical irritation is probably not primary but a jagged tooth will give leukoplakic tissue access into the mesoderm, much as a razor nick stimulates an actinic keratosis. Avitaminosis A is importantly concerned, as is also the complexion of the patient, for squamous carcinoma, *wherever it occurs*, preferentially (not invariably) attacks persons with the reddish tint in their coloring Tobacco distillates irritate the mouths of these people more than they irritate the mouths of others. The interaction of factors involving vulnerability nutrition hormonal balance and various other incitations to malignancy is evident in leukoplakia and carcinoma of the mucous membranes. Xerostomia in women (p. 1032) and kraurosis (p 1031) require reference in this connection

Leukoplakias of the larynx trachea bronchi, bladder ureter, renal pelvis, vulva, vagina, cervix uteri, uterine mucosa, glans penis, anal mucosa and rectum are alike (David: APath 26 151 1938) Wherever squamous carcinoma begins on a surface supporting stratified squamous epithelium—stratified squamous in type perhaps because of irritation and metaplasia—the initial lesion is intraepidermal and is leukoplakic or erythroplakic. While this early superficial lesion may be obscurely situated, in a fissured or chronic granulomatous lesion, it is there and can be demonstrated by discerning investigation.

Normal and abnormal epithelia grow where they can grow spreading in sheets, covering surfaces insinuating into crevices. Abnormal epithelium supplants the normal and may spread widely before its cancerous nature becomes clinically apparent

This fact especially concerns the oral lesions which surround teeth. To pull the tooth allows leukoplakic, superficial carcinoma to gain access to the cavity as it granulates, and even to reach the cancellous spaces of the jawbone. If one destroys *all* of the leukoplakic epithelium with the cautery at the time of making the extraction, the epithelium that grows over the denuded region in the course of healing is normal epithelium, and carcinoma is avoided. To extract teeth surrounded by and embedded in, leukoplakia is to ask for trouble in the form of promptly developing and invasive carcinoma, unless these facts are kept in mind.

Oral hygiene, considered to be of some importance by Sturgis and Lund (NEngJM 10: 996, 1934) in their study of etiology in 620 cases of leukoplakia, probably is tied up with avitaminosis, for the person with a filthy and neglected mouth is likely to have dietary inadequacy too. Betel nut chewing provocative of irritation of the mouth by lime cheap tobacco areca nut, and flavors such as catechu, cardamon, and nutmeg, is an etiologic factor in cancer of the mouth in correlation with avitaminosis (Orr: Lancet 2: 575, 1933)

Sturgis and Lund listed these factors tobacco, dental irritation, dentures, oral hygiene, syphilis, avitaminosis A and inherent susceptibility McCarty (InternatJM&S 47: 89 1934) discussed faulty occlusion, chronic irritation tobacco and syphilis. The importance of tobacco is apparent to any clinician who has successfully prevailed upon a leukoplakic patient to discontinue its use. Many a carcinoma has developed beneath the end where it is habitually held in the corner of the mouth cancer having failed to develop

from leukoplakia on the other cheek. The cancers of chutta smokers and the gingival trough cancers of those who place khaini (tobacco and lime) between the lower lip and the teeth) were described by Khanolkar and Suryabai (APath 40: 351, 1945)

Syphilis is a cause of leukoplakia. The atrophic scar of a syphilitic oral sore is whitish, but not with neoplastic leukoplakia. Neoplastic leukoplakia grows more favorably in syphilitic oral lesions than in otherwise normal mouth and the coincidence of gumma and carcinoma of the tongue has long been recognized. One wonders whether the cancer may not sometimes localize the syphilitic process as the syphilitic ulcer may promote the progress of pre-existing superficial neoplasia.

PATHOLOGY.—The histologic structure of neoplastic leukoplakia is that of keratosis senilis with the added factor of continuous wetness.

McCarthy (1934) attempted to establish these grades I lesions at first reddish, sharply defined slightly sensitive becoming whitish gray manifesting no microscopic proliferation II, patches lacking palpable induration, but manifesting hyperkeratosis, acanthosis and slight evidences of inflammation III milky white pearly indurated lesions, with considerable inflam-





Fig 1606.—Leukoplakic superficial squamous carcinoma, in chin lip and gum.
Fig. 160 —Leukoplakic early squamous carcinoma. (Dr Fred Weidman.)

mation and IV fissured or warty lesions manifesting their incipient carcinomatous nature by early erosion and induration. McCarthy recognized the similarity to cutaneous keratoses the invariable development into squamous carcinoma when carcinoma develops, and the variability of degrees of malignancy

There is no distinct dividing line between lesions malignant and precancerous. The experienced practitioner especially if he is experienced with microscopy knows what to expect of a given lesion. Persons unfamiliar with the minute structure of the diseases they meet have no business treating them—neoplasia of the mouth especially where error is disastrous—and this statement is intended specifically to apply to those who wish their microscopy supplied for them secondhand in the sugar-coated form of grades.

A carcinoma of the mouth or elsewhere superficial or deep, is as malignant as its most malignant part It is easy to destroy it in its totality early late the carcinomas of the mouth are the worst with which the dermatologist may be called upon to contend.

DIAGNOSIS.—The history character repetitious scaling and tedious course of the lesion should serve to distinguish it from lupus erythematosus, lichen planus and mucous patches. As a rule neither lichen planus nor secondary syphilis involves the mouth alone. Cases involving the vulva must be distinguished from kraurosis, moniliasis, lichen sclerosus, and lichenification. Schiller s iodine test has some practical utility in determining the extent of leukoplakia of the buccal mucosa as well as of the cervix; see bibliography hereinafter on early cancer of cervix uteri.

TREATMENT of neoplastic leukoplakia is, best to destroy it with the ac tual cautery Destruction does not need to be deep but must be wide to include all of the patch missing no square millimeter of it One intends that replacement of the loss shall take place by proliferation of normal epithelial cells lying beyond the periphery of the abnormal area. If this necessitates denudation of half of the buccal cavity it must be done in one operation An extensive area may be destroyed with surprisingly little morbidity During healing of the burn, bland soft foods and nonirritating mouthwashes are prescribed, along with perhaps, an antibiotic to be swallowed for its systemic, not local effect. Pain is not great. Fulgurating or diathermic devices are not so satisfactory as the actual cautery X rays and radium are not satisfactory in treating intraoral superficial neoplasia.

Any means for destroying epithelium can be used with success, but the easiest is the cautery Solid carbon dioxide has been so used. Acids of one kind or another could be used but I believe that they should not Applications of silver nitrate are especially successful in promoting the progress of leukoplakia into carcinoma.

Cessation of the use of tobacco is imperative. Some patients have the character to achieve this, when given sound reasons for doing so others are not able The easiest way to stop is to stop outright. One is likely to gain 10 pounds in weight. The improvement in a leukoplakic mouth after a month without tobacco is always striking

The teeth should be scaled and kept clean. Rough edges should be ground smooth, and cavities should be repaired. Protheses should be maintained in first-class condition, well fitted, without rough edges. Progressive leukoplakia growing about pyorrheic and abscessed teeth is always a difficult problem. Such a situation calls for cooperation between the extractionist and whoever treats the leukoplakia so that it may be destroyed *immediately* after the tooth is removed.

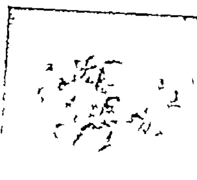
Attention to diet may be advisable. Following the administration of vitamin A concentrates, benefit results in some cases.

When the transition of intraepithelial neoplasia into intramesodermal carcinoma seems to have been passed treatment is as for carcinoma. As Hertzler has said To treat, or better to tease an ulcer of unknown nature is to do something that should not be done A biopsy is something to make the judicious grieve, stupid timidity If the lesion is small the whole thing should be removed, if it is too large to remove completely diagnosis certainly can be made at clinical examination. A slide can be obtained for record without detriment to the patient, at the moment when treatment is begun. To cut out for microscopic confirmation a piece of a lesion which screams its identity is preposterous.

Erythroplakia.—Some keratoses spread centrifugally in a considerable area before neoplastic cells, previously lost by exfoliation, eventually find within the dermis a fertile medium where they speedily produce obvious carcinoma with infiltration, invasion, ulceration and metastasis. When this process occurs on a mucous membrane the lesion is called erythroplakia. It is a sharply marginated, irregular velvety reddish plaque with thin and fragile epidermis bleeding readily when subjected to friction, as described by Sulzberger and Satenstein (ADS 28 798 1933) Irgang and Alexander (ADS 34 247 1936) and others. Analogously on the skin or glans,

Paget's Disease.—All of the original cases of Paget (St Bart Hosp Rpts 10 87 1874) occurred in women between 40 and 60 years of age and involved the region of the nipple. Males also are attacked, and the disease is not confined in location to the mammary region. This carcinoma begins insidiously





Figs 1408A and 1408B.—Bowen disease.





Fig. 1409A.—Bowen disease. (Dr John C. Belisario.)
Fig 1409B.—Erythroplakia of Queyrat. (Dr John C Belisario.)



Fig. 1410.—Intra-epithelial carcinoma of areola and nipple Bowen's type

with a sharply circumscribed inflammatory eczema of the nipple and contiguous areola or other locale. There may be slight scaling at first. Later the exudation of sticky viscid fluid leads to more or less crusting. Itching is an early symptom. The lesion does not respond to treatment for inflammation and never heals spontaneously

The majority of the breast cases occur in middle-aged or elderly women who have borne children. The right breast is affected more frequently than the left.

The unity of the eczematoid disorder and the carcinoma which obviously follows it was long disputed. Cheatle (BritJSurg 11: 295 1923) who made histological examinations of 8 affected breasts, believed that Paget's disease of the nipple is a primary malignant disorder and that glandular carcinoma of the breast is a secondary process although



Fig. 1611.—Noncoherent intraepithelial carcinoma constitutes in this case a "senile keratosis." Lesion from the cheek.



Fig. 1612.—Intraepithelial carcinoma: parakeratotic corneum from cancer cells.
Fig. 1613.—Paget's intraepithelial carcinoma.

it primarily arises in the epithelial cells of the gland. Some have held that the dermatitis is primary and the carcinoma secondary; others, the reverse. Arguments pro and con have been summarized by Hertzler (Treatise on Tumors, New York, 191). In favor of the primary nature of the skin affection may be mentioned: (1) the disease may exist many years before carcinoma can be demonstrated; (2) similar lesions are found on the penis, scrotum, vulva, and umbilicus; (3) peculiar cells (Paget cells) are present in the epidermis; (4) the continuation of the epidermal cells into the carcinoma is apparently direct. In opposition to the primary nature of the affection are these arguments: (1) early involvement of the

cells lining the ducts is demonstrable, (2) the tumors when first discovered are deep and may retain a glandlike contour; (3) the Paget's cells may result from metamorphosis of epidermal cells from the deeply lying carcinoma; (4) eczema of the nipple may exist without the development of carcinoma.

In breast cases, the point of origin of the intraepithelially spreading neoplastic cells may be within the breast, within the nipple, or on the nipple or the areola. Elsewhere, the lesions look like superficial carcinoma, simulating erythroplakia or keratosis senilis on the lip or superficial basal cell carcinoma on the trunk the oozing, eczematoid character is preserved. The extent of the spread over the nipple and areola is inversely proportional to the

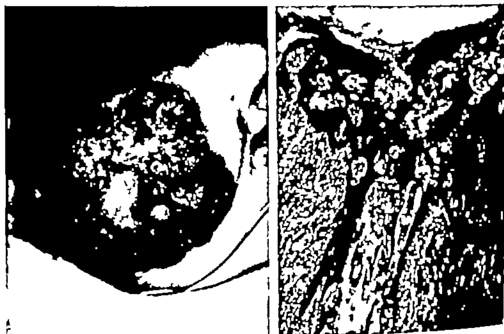


Fig. 1614.—Paget' disease of breast (Dr Sam E. Sweitzer)
Fig. 1615.—Paget's carcinoma in epidermis and duct of nipple.



Fig. 1616.—Dermatitis of areola resembling Paget disease, from which was cultivated hemolytic *Micrococcus aureus*.

depth of the point of origin within the breast and directly proportional to the duration of the lesio 's existence. If examined with this in view a large proportion of carcinomas of the breast will be found to manifest a small area of eczematous, intraepithelial, carcinomatous involvement of the pple.

Cl nicians sometimes debate whether Paget's disease occurs elsewhere than on the breast, and wh h f the possible sites of inception the title should be applied to: in the breast with extens n outward through the nipple and over the areola; in the nipple with extension onto th kin and into the breast; or in the skin with extension through the n pple into the d t Su h argument seems trivial to th hl tologist who sees the same process of intraepidermal carci omatosis constituting eczematoid neoplastic disease on the

lip, in occasional senile keratoses, and on various parts of the body Sutton (ADS 46: 1 1942) described the clinical varieties of neoplasia as they are related to the rate of growth and cohesiveness of the parenchyma.

Paget s disease is that type of epidermoid carcinoma wherein the cells are not coherent and are usually of rapid growth rate though not invariably so It is a biologic process of symbiosis of epidermal cells and cancer cells which are large sharply defined and uninucleated, possessing deeply staining nuclei and retracted, faintly staining protoplasm (Muir JPathBact 49 299 1939) The cancer cells spread intraepidermally in small groups or even singly They gradually extend peripherally and in breast cases deeply along the ducts, metastasizing early In Paget s disease of the nipple amputation of the breast should be performed at once.

The disease is carcinomatous from the beginning it is generally believed. This view was held by such authorities as Jacobaeus (VirchArch 178 124, 1904) Kaiser (VerhandlDeutschPath-Ges 17 328, 1914) Sekiguchi (AnnSurg 65: 175, 1917) who reviewed 200 cases Muir (JPathBact 30 451, 1927); Pautrier et al. (ADS 17 767 1928); Miller and Anderson (J 94 1083, 1930); Fraser (NYSJM 30 13, 1930) Muir (BritJSurg 22: 728, 1935) Inglis (Paget Disease of the Nipple and Its Relation to Surface Cancer and Precancerous States, Oxford U Press, 1936, 232 pp.); Pinkus and Gould (ADS 39: 479 1939)

Extramammary Paget's Disease has involved the lip vulva and penis, where clinical resemblance to erythroplakia (q v) is considerable, and the scrotum, perineum pubes, umbilicus, nose, forearms and trunk.

According to Hartzell (JCutD 28: 379 1910) the first extramammary case reported was that of Morris (1880) involving the neck, while Crocker (1889) observed penile and scrotal cases. Hartzell's patient was an old man with a palm-size lesion on the arm. The back was involved in that of Towle (JCutD 30: 286, 1912) the axilla in that of Satani (BJD 32 117 1920) who found 30 extramammary cases in the literature at that time. Beet (BMJ 43: 235, 1923) described involvement of the ears, nose and mouth. Drake and Whitfield (BJD 41: 177 1929) recorded a vulvar example, and Bussman and Woodburne (ADS 4 296 1931) reported one of the glans penis. An old woman with a large, crusted lesion of 4 years duration on the thigh was reported by Harding (JPathBact 35 295, 1932) and the groin was the site in a similar patient of Dörffel and Grimm (DWchn 101: 1169 1933) Weiner (AmJCanc 31: 373, 1937) found 57 extramammary cases in the literature and added a vulvar one which led to the patient s death after 10 years of dilatory mismanagement. The subject was reviewed by Parsons and Lohlein (APath 36: 424, 1943) who were conservative in accepting the veracity of reports but acknowledged the correctness of the diagnosis in many cases.

Prognosis and Treatment —In early breast cases, the outlook under proper treatment is good. In advanced cases the prognosis is that of highly malignant carcinoma. While encouraging results have been reported following the use of x rays and radium, excision which is prompt and radical is best and surest. In extramammary cases, lesions resembling senile keratoses may successfully be blistered off Fulguration is apt to allow missed cells access to the dermis then they grow as squamous carcinoma.

See Wiggin and Fordyce (NYSJM 66 445, 1897) Pautrier et al. (BSocfrançD 31 114, 1924); Arndt and Kren (ADSyph 148 234, 1924-1925), Krembelmer (MünchMWchn 72 840, 1925); Milian (BSocfrançD 33 662, 1926) Semmes (BritJSurg 15 635, 1928); Rubenstein (ADS 22: 281 1930) in male, bibliography Kaiser (DWchn 101: 1441, 1935) Cheatle (SGO 66 575, 1938); Muir (JPathBact 49 299 1939) histology West and Nickel (AnnSurg 116 19 1942) 12 nipple cases, review; Metrovsky and Keys (BJD 57: 212, 1945), cytology Schwartzmann (SouthMJ 46 1107, 1953) anal lesion causing pruritus Huber et al. (AmJOb-Gyn 62 778, 1951) vulvar involvement requires simple vulvectomy Soeck (Dermatologica 102 161, 1951) vulvar; Bowman and Hartman (Arch Path 58 304, 1954) vulvar, Pinkus (J 156 736, 1954) extramammary cases not extremely rare; Plachta and Speer (Cancer 7: 910, 1954) vulvar case apparently originating in apocrine gland.

CUTANEOUS HORN

Hornlike epidermal growths composed of corneous material originating from a circumscribed zone of abnormal epidermis are somewhat rare. They do not overlie a bony frame as do horns of cattle They represent marked cohesiveness of keratin, and arise from corns, calluses, congenital epidermal de-

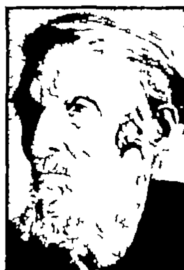




Fig. 1617.—Cutaneous horn. (Dr. J. D. Kessler.)
Fig. 1618.—Cutaneous horn, natural size. (Dr. J. D. Kessler.)





Fig. 1619.—Cutaneous horn of lip. (Dr. John W. Perkins.)
Fig. 16 0.—Cutaneous horn of right cheek.





Figs. 1621 and 1622.—Cornual squamous carcinoma f helix, nd section of it showing coherent carcinomatous origin.



Fig 1423 — Astonishing case of cutaneous horns a 17-year-old white girl of South West Africa. (Walker BJD 59 34, 1947)

CARCINOMA OF THE SKIN

Carcinomas are made up of epithelial parenchyma and connective tissue stroma. The stroma may consist largely of newly formed tissue, as in pedunculated and expansile growths, or it may be derived from both old and new fibrous tissue, the former being supplied by the involved organ, and the latter by proliferation of pre-existing connective tissue. The active agent is the living neoplastic epithelial cell. All manifestations are secondary to it and dependent on it. In general, the more rapidly a carcinoma grows, the less its cells resemble normal ones and the more intense the inflammatory reaction it induces.

Classification.—Cutaneous carcinomas are classified according to the types of cells which their cells resemble. See Pinkus (JMichSMS 37: 533, 1938) Beerman (AmJMedSci 211: 480 1946) Welton et al. (ADS 60 277 1949)

Squamous (Epidermoid) Carcinomas are epithelial blastomas with cells like those of the rete they are characterized by the keratinization of their decadent cells so as to form pearls within the larger aggregates and by their capacity for metastasizing

Basal Cell Carcinomas are growths not metastasizing composed of small, deeply staining epithelial cells of various sizes and shapes, the congeries of which bear more or less resemblance to the epithelial tissues of the pilosebaceous organs.

Transitional Cell (Baso-squamous) Carcinomas are epidermal tumors composed of an admixture of basal and squamous cell architecture, which may or may not be homogeneous. These lesions resemble too closely the structure of other basal cell tumors to warrant their segregation into a special oncologic entity according to Welton et al. (ADS 60 277 1949)

Bowen's Disease (q v) is a variety of anaplastic squamous carcinoma with pallid, irregularly hyperchromatic cells of variable size, forming in the early stage crusted lesions resembling senile keratoses and comprising in fact a small proportion of such lesions.

Paget's Disease (q v) is a variety of malignant carcinoma in which the cells are hydropic and noncoherent and in the early stage permeate the epidermis diffusely and in small groups, producing exudative lesions simulating dermatitis.

Melanocarcinoma is the malignant cancer arising from the pigment producing cells found mainly in the epidermis (see Melanoma)

Anaplastic Carcinomas, composed of loosely aggregated cells which undergo individual rather than group keratinization, are members of the squamous type comparatively highly malignant. See Sachs et al. (ADS 59: 263 1949)

Spindle-Cell Carcinomas are a form of squamous carcinoma wherein the cells are of spindle shape, simulating those of some sarcomas. They generally appear in scarred tissue such as may result from x ray injury or lupus vulgaris. Martin and Stewart (AmJCanc 24 273 1935) reported 8 cases, 4 of which were fatal and called attention to the similarity to sarcoma

Sarcoma following x ray injury is in fact spindle-cell carcinoma as a rule (Sims and Kirsch ADS 57: 63, 1948) although Dentlcke (BeitrKH Chi 169: 14, 1939) reporting 3 cases and reviewing the literat re pparently missed this fact. Carcinosarcoma was reviewed by Saphir nd Vass (AmJCa c 33: 331 1938) who were dubious of almost all reported cases. Pack and Wuester (J 113 879 194) studied 4 cases of this type along with other carcinomas beginning in scars. Th differentiation from sarcoma is frankly difficult i some cases (Brooks: APath 36: 144 1943) F ve cases i volving individuals not previously exposed to x ray were reported by Strauss (ADS 61: 633 1950), some of which seem to me to ha e been basal cell carcinomas, in which spindle-shaped cells re commonplace In the 40 cases collated by Underwood et al. (ADS 64: 149, 1951) the linical appearance was not distinctive although the lesions were ften nodular ulcers or f gating. They were found more often on the head than on the extremities, were generally solitary and were capabl of producing multiple metastases in the skin, lymph nodes nd viscera. Reticulum-staining failed to distinguish them histologically from sarcoma, they found, confirming the observations of Brooks (1943) They require radical treatment.

Transition of mouse mammary adenocarcinoma into spindle-cell carcinoma in subsequent generations was observed by Ehrlich and Apolant (BerlKlinWchn 42: 871, 1905) and Goldfeder and Nagasaki (CancRes 14 267 1954)

Malignancy a descriptive term, refers to capacity for and speed of doing harm. The word may be restricted in meaning to signify a capacity for metastasis in contrast with a capacity for merely local growth. It is generally loosely used epistemology in these hurried times is a discipline too much neglected.

Malignancy should be a strictly clinical word the microscopist can only say that he thinks the tissue came from a lesion which would behave as a malignant tumor (Sutton ADS 46 1 1942) The rate of ulceration is related to malignancy being roughly directly proportional except in highly malignant lesions, where invasion is rapid and only small central ulceration appears, until late (Wilson ADS 41 667 1940 Broders grading) The size of the lesion when treatment starts is inversely related to curability Warren and Hoerr (SGO 69 726 1939) reported 7% mortality from lesions 1 cm. in diameter or smaller 82% mortality in lesions 5 cm. in diameter or larger See prognosis (p 1224)

Metastasis is the transplantation into a new site distant from the primary field of growth of neoplastic cells capable of continued proliferation. Lymph nodes are reached perhaps by insinuation of a narrow strand of growth, perhaps by ameboid movement of the cancer cells themselves, but most likely simply by currents of the lymph and tissue juices, which depend on normal drainage and muscle movements. The lungs liver and other structures are generally reached via the blood stream. See Metastatic carcinoma. Cancer cells breed true those in the metastasis are exactly like some of those living in the primary lesion

Metastasis may not be detectable at the time the primary tumor is eliminated. The appearance of metastases after seeming cure of a lesion is hard to explain to the laity who tend to believe the operative procedure caused it and to blame the physician. The average patient is better informed nowadays than he used to be, but a physician is wise to expend effort on explanations before he actually treats a case in order to forestall problems which might otherwise be troublesome later

Recurrence of a tumor which has been excised or otherwise destroyed is interpreted indubitably to imply that not all cancer cells were reached in the initial therapeutic effort A frequent cause of recurrence *after* treatment of cancer of the skin is the failure to recognize the fact that leukoplakia or keratosis surrounding an ulcerative carcinoma is a part of it, a part superficially located and not as yet intradermal, but composed of the same breed of neoplastic cells. The two commonest errors made in treating cancer of the skin are (1) to fail to take enough and (2) to attack from the center outward. One should sacrifice normal tissue three-dimensionally peripheral to the entirety of the lesion by an enveloping amputative maneuver (Sutton: ADS 68 154 1953) This is the *en bloc* principle, now accepted generally

The skin is an organ in which the appearance of more than one tumor representative of individual phenomena is commonplace An experienced dermatologist can name a number of his patients from whom at various times he has removed a dozen or more isolated malignant lesions. It is certainly possible for a new one to develop near the site of a previous one without being in reality a recurrence thereof See Multiple tumors (p 1203)

Mode of Onset.—A lesion which has arisen from a pimple which the patient mistook for a whitehead and squeezed is likely to be basal cell tumor A lesion which developed from a scaly place which scaled off repeatedly and finally began to bleed usually proves to be squamous, particularly if it arose on an exposed area of a sun sensitive skin.

EARLY SQUAMOUS CARCINOMAS are described with senile keratoses (p 1155)

Early Carcinomas of Mucous Membranes, which are of malignant character and rapid development because of the loose and well nourished tissue into which they are free to grow arise usually from malignant leukoplakia or erythroplakia of mucosae of the lips, tongue, gums and elsewhere. They either ulcerate or vegetate invasion signifies high malignancy while heaping up portends evil that is less urgent. Early mucosal carcinoma is discussed with Leukoplakia (q v)

Early Basal Cell Carcinomas are described with epithelioma adenoides cysticum (q v) Carcinomas of the cutaneous accessory structures are usually of the basal cell type.

Multiple Tumors occurring simultaneously may result from multiple pilosebaceous anlagen, yielding basal cell tumors, or grow from senile keratoses, yielding mainly squamous cell tumors.

See Epithelioma adenoides cysticum, Senile keratoses, Xeroderma pigmentosum Phillips (SouthMJ 35 883, 1942) described 704 microscopically verified skin lesions obtained from 210 patients Cooper (SurgClinNoAm 24: 1032, 1944) reported on 106 cases. See W rren and Gates (AmJCanc 16 1260, 1932), 1269 cases collated, 3.7% incidence in cancer topsies Burke (AmJCanc 27: 316, 1936) Kirshbaum and Shively (JLabClinM 24 282, 1938), review ing 16,370 autopsies Stalker (SGO 68 698, 1939); Sutton (ADS 42 838 1940) Tullis (JLabClinM 27 688, 1942)

Location is to some extent correlated with the type of tumors one may expect to find. Howles (SouthMJ 28 494 1935) reviewed some 2,200 cases of cancer of the skin as to location and Sutton (JMoMA 39 203 1942) analyzed 560 basal cell tumors from a collection of 1,500 specimens representing 36 varieties of new growth.

Face.—About half the cases are squamous nd half basal. A majority of those on the uppe lip, nose d forehead are basocellular Ward and Hendrick (AmJSurg 79: 771, 1950) reviewed 840 cases of head and neck epithelioma. Of 247 cases of Palit schewsky (Ztsch Krebsfor 40 159 1933) 49% were basal cell. Laymon (JLancet 56: 472, 1936) treated 63 cases by x ray to his satisf ction. See Blair et al. (Cance of the Face and Mouth, Mosby 1941) Schrek and Gates (AP th 31: 411; 422; 434, 1941) reported on 2,580 lesions, 1,527 of which were basal cell and 1,053 squamous; of the latte 70% occurred in males.

In a series of more than 800 cases Roland and Lain (SouthMJ 20 794 1927) found that 5% of the patients were under 35 years old; 56% were between 35 and 55 years, and 39% were older tha 55 years. The sex ratio was 7 men to 3 women. In their cases, the cheek was i vol ed in 25% the nose in 24% a d the lower lip in 17% the remaining 33% being distributed in 21 different local ties.

Nose.—A large majority of the epitheliomas here are basal cell. I much prefer surgical therapy for them. See Sutton (J 77 1561 1921) rad um and surgery; Robinson and Harris (AmJRoentg 43: 59 194_)

Ear.—The large majority are squamous (Lunsford nd T ewig: CalifWM 25 740 1926) Surgery is advised beca se a curati e dose of radiation will also destroy cartilage (Drive and Col AmJRoentg 43: 66, 1942)

Tumors of the skin of th external uditory canal collected by Mitchell (AOtol 32: 831 1940) included 1 resembling a cylindroma, a keloid, 5 osteomas, a nonspecific ulce d 3 squamous carcinomas. Scott and Colledge (ProcRoySocM 32: 1097 1939) collected 70 cases. Ten cases, 9 of them in males, of primary carcinoma of the eusta hian tube were found by Stewart and Lieber (APath 30: 518, 1940) See ceruminous gland carcinomas.

Scalp.—Cysts and nevi are commonest and squamous carci oma may evol e from a en. Seborrheic keratoses melanoma, lipoma, basal cell carcinoma and metastatic lesions in the skin are also seen (Love: MP&Circ 212 196, 1944) An unusual case of multipl squamous carcinomas of the scalp was reported by Stout (JM Ma 46: 259 1949) See syringomas (p. 1165) and apocrine cysts of the scalp (p. 1171)

Eyelids are the seat of several kinds of tumors in addition to inflammatory new growths chalazion denoma or carcinoma of the meibomian gla ds papilloma, nevus, hemangioma, sebaceous cyst, sudoriferous cyst, and fibroma. Basal cell carcinomas are commonest. Surgical treatment is usually preferred (Hollander d Krugh: AmJOphth 27: 44, 1944) although with proper protection of the eye, radiation can be accomplished with excellent effect (Driver and Cole: AmJRoentg 14: 616 1939; Hunt: 57: 160 1947)

See Lebensohn (AmJOphth 18: 862, 1931) tumors of meibomian glands; O'Brien and Braley (J 107 933, 1936) 100 cases, various; Birge (AOphth 19: 700, 1938) 171 basal, mixed nd squamous carcinomas; Birge (AOphth 20 254, 1938) 230 cancers Sharp (J 111: 1617, 1938) radiation therapy Martin (AOphth 22: 1, 1939) low- oltage technic; Stroud and Stew rt (TexasStJM 36 420, 1940) epithelial tumors of eyelids, treatment; Saulther (BritJOphth 24 105, 1940) x ray therapy; Evans (AOphth 24 83, 1940), lacrimal caruncle, 200 cases, growths various as of the skin; Samoode (APath 31: 789, 1941) arieties; Ash and Wilder (AmJOphth 25 926, 1942) lesions, usually squamous; Hilt (Tumors of the Eye and Adnexa, in Tumors of the Head and Neck, Ward and Hendrick, Williams & Wilkins, 1950)

monographic, well illustrated; Duke-Elder (Textbook of Ophthalmology Mosby 1952 pp 5029-5118) exhaustive Seale (ADS 68, 216, 1953) limbus, 19 carcinomas treated successfully with radium; Traub (J 154: 9 1954) radiation therapy

LIPS.—Lesions originating on the vermilion portion of the lower lip are squamous. The starting place is the line of closure where saliva is desiccated and tobacco tar in smokers, is concentrated; this line is not the mucocutaneous junction. The lower lip supports the vast majority of lip carcinomas because of its exposure to sunlight (Molesworth: DWehn 99: 1134 1934) and males are subject to this disease 50 to 100 times as frequently as females (Hunt NebrMJ 25: 183 187 1940) In a study of 537 cases of squamous carcinoma of the lip, Broders (J 74: 656 1920) found that males were attacked 49 times oftener than females. The average age of his patients was 57 years. Farmers comprised 56% of the total. About 8% of the patients were tobacco users. The lower lip was affected in over 95% of the cases.

A model of serial sections made by Warwick (J 82 1119 1924) showed the interesting structure of a lip cancer which arose as a number of projections from multiple points in the surface

Lesions originating in the skin near the mucocutaneous junction are usually of basal cell nature Basal cell tumors of the skin of the lips received attention from Pusey (JCutD 31: 73 1913) and this tumor extended into the mucosa in 4 of 106 lip cancers reported by Bloodgood (J 55 1615, 1910) who found that of 13 lesions of the upper lip, 9 were basal cell. See Borrmann (ZtschrfChir 6: 404, 1905) Delarue and Favera (abs ADS 39: 354, 1939) studied 32 upper lip cancers, which occur more often in women than in men (Schamin: abs JIL 1641 1930) A large proportion of epitheliomas of the upper lip in the female are basal cell. I removed one from a girl 6 years old.

MOUTH AND TONGUE.—Epithelial tumors are always squamous except the rare granular cell myoblastomas and tumors of the salivary gland (see *mixed tumors*, p. 1262) Neoplastic lesions seen in the mouth include neurofibroma, angioma, cyst, myeloblastoma, adamantinoma, etc. Martin (ASurg 44 599 1942) collected 93 cases of tumors of the palate A malignant adenocarcinoma of a mucous gland was reported by Lepp (BeitrzpathAnat 10 164, 1939) Squamous carcinoma was present on the tongue of a newborn, reported Frank et al AmJCanc 26 5 1936) and was fatal to a boy only 15 years old, a patient of Salechy (AmJCanc 38 257 1940) who found 8 similar cases.

EXTREMITIES.—The large majority of the lesions occur on the dorsa of the hands, and these are generally squamous in type basal cell lesions in this location being rare although 6 were seen by Braddon (MJAustral 1 368 1944) Actinic and x ray dermatitis are common causes. Most of the lesions on covered parts of the extremities are basal cell tumors (Sachs and Garbe ADS 36: 278, 1937) Half of all malignant melanomas (q v) originate on the soles.

Correlating the size and prognosis in 27 cases of squamous carcinoma of the dorsum of the hand, Clark and Johnson (JKansMS 49: 100 1948) reported mortality over 50% if the primary were 5 cm. in diameter or larger and at 3 cm. the lesion was highly dangerous. If the invasion of squamous cancer of the hand reaches the depth of the coil gland bodies, the lesion is dangerous in 70 cases of Johnson and Ackerman (AmJPath 23: 791 1949), of those which did metastasize all extended below this level, the explanation probably being the absence of mechanical tissue resistance deep in the skin. Cancer of the skin of the extremities accounts for not over 1% of all cases (Characho: SGO 68: 1002, 1939).

See Mason (ASurg 18 2107 1929) 25 cases added to 241 in literature of carcinoma of the hand DeBall and Stevenson (SGO 63 222, 1936) 61 carcinomas of upper and lower extremities, commoner in male, majority on hand Mason (SGO 64 129, 1937), varieties of tumors of hand Schafft (ZtschrKrebsforsch 49 1 1939) trunk and extremities; Mason (Surg 5 27 1939) hands and feet Campbell (ASurg 43; 603, 1941) 26 cases upper extremity, Spencer (ADS 44 214 1941), squamous cancer of leg of Negro Taylor et al (AmSurg 113 268, 1941) lymphatic metastases of cancer of extremities, prefers to wait for clinical evidence of involvement Clifford and Kelly (PlastReconstrSurg 12: 227 1953) hand

PENIS.—Lesions here are squamous. They sometimes begin in the *form of erythroplakia* (q v) Unabbreviated foreskins predispose (Plaut and Kohn-Speyer Sci 105 391 1947) Since cancer of the penis does not occur in persons who have been circumcised early the disease is a preventable one (Handley BMJ 2 841 194); interestingly the incidence of carcinoma of the cervix uteri is low among the wives of men who have been circumcised. Prophylactic circumcision during infancy should be routine (Bleich: J 143 1054, 1950) *Cancer of the penis comprises from* 1 to 3% of cancer in males (Harlin JUrol 67 326, 1952) the 2 clinical types being papillary and infiltrative. *Granulating* and fungoid lesions are occasionally seen and are of low malignancy (Buschke and Loewenstein KlinWchn 4 1 6 1925 Traub: ADS 40 159, 1939) and in general the disease is slow to metastasize simple amputation being often adequate to cure (Nesbit and Keitzer SGO 63: 504, 1936) A fulminating case evolved from a crusted lesion of the sulcus to a fatal termination in 4 months in the unusual case of Ormond (J 114: 1546, 1940) In 1 instances of penile fibrosarcoma there were of associated carcinoma in the collection of McDonald and Heckel (J 154: 993 1954) See smegma in etiology (p. 1 16)

A remarkable monograph is that of Matsumoto (Carcinoma and Precancerosis of the Male Genitals Kyoto U Press, 1951)

The treatment is surgical (Carlson: JUrol 44 307, 1940; Bassett: Cancer 5: 530 1953) and the lymph nodes must be attacked surgically if they are involved, although distant metastases are rare.

Scrotum.—Here the *lesions are squamous, and are usually related to occupation.* Henry (AmJCanc 31: 28, 1937) found 1,437 fatal cases in England and Wales in the period 1911 to 1935, and all but 13 were carcinomas. Of 103 cancers in chimney sweeps, only 44 were not scrotal. All cancer deaths in chimney sweeps which occurred before the age of 45 years were due to scrotal carcinomas. See Graves and Flo (JUrol 43: 309 1940)

Vulva.—Squamous carcinoma is the usual variety of the rare carcinomas here. Syringoma (q.v.) is a more common tumor and others in this location incl de fibroma, lipoma, hemangioma, endometrioma, cysts and melanoma (*Taussig: AmJObGyn 40 764,* 1940; Folsome: J 114: 1499 1940) Two leiomyomas and 1 ganglioneuroma were among the 84 cases of benign tumor of the vulva collected by Lovelady et al. (AmJObGyn 42 309 1941) Basal cell carcinoma of the vulva is quite rare; 4 cases were added to 23 found in the literature by Wilson (ASurg 43: 101 1941) Carcinoma of Bartholin s glands (q v) may occur Of the 37 cases of primary carcinoma of the vagina studied by Emmert (AmJObGyn 36: 1055, 1938) 11 were of the squamous variety and we e ulcerative or papillary Palmer and Biliback (*AmJObGyn 67: 877 1954*) reported *112 cases. A diffuse* primary adenocarcinoma of the vagina, an unusual tumo occurred in a Negress seen by Piper (AmJObGyn 40: 493, 1940)

Since cases are rare and records of 5-year arrests disappointing Way (BMJ 2: 780, 1954) urged that the patients be placed in the hands of selected surgeons for the radical surgery that must be undertaken. He reported 5-year survivals of 85% in cases without lymph node involvement and of 45% in those with it when treatment was adequately radical by current standards.

See Twyman and Nelson (JMoMA 23 165, 1926) surgical treatment; Drant (PaMJ 43: 1405, 1940) vulvectomy and indications; Smith and Johnson (SouthMJ 47 170 1954) 55 cases of vulvar carcinoma, radical surgery with 60% 5-year survival rate.

SQUAMOUS CARCINOMA

Symptoms.—An epidermoid or prickle-cell carcinoma is a malignant growth originating in epithelium and characterized by cells resembling those of the squamous layers of the epidermis in that they undergo keratinization when they degenerate. Their histogenesis is described under Superficial neoplasia (q v) Pain is not a prominent feature until late in the disease. The earliest perceptible lesion in squamous cancer of the skin is a roughened, warty keratotic patch or senile keratosis, or a small, reddish or yellowish, circumscribed nodule from the center of which projects a horny spike. In a few weeks or months the dermis becomes infiltrated so that thickness is pal pable Eventually the midportion of the gradually enlarging growth ul cerates. The superficial ulcer is at first partially hidden by scales and crusts. The base is always sharply defined, and more or less indurated reddish because of dilation of congested and inflamed capillaries.

The lesion increases in size by peripheral extension and increment of central ulceration. The edges of an advanced tumor usually become hard everted and undermined. As the growth extends, connective tissue, cartilage periosteum and bone are attacked. Lymph node *involvement follows sooner* or later the tumors evincing great individual differences in their ability to metastasize and their rapidity in doing so. The development of secondary tumors in internal organs is an occasional sequel.

Most patients are middle-aged or elderly individuals. The sites of predilection are the face particularly the lower lip ears, and dorsa of the hands. Vegetating carcinoma may be papillomatous from the beginning, or it may develop from an ulcerative lesion, becoming cauliflower like, with a verrucose surface covered with tenacious, foul-smelling, yellowish, purulent exudate. Comparatively benign, pseudoactinomycotic lesions are occasionally seen (Charache ADS 43: 809 1941) see also Carcinoma location (p 1203)

Carcinomas of the Mucous Membrane, malignant squamous carcinomas, af fect mucosae of the tongue buccal, oral and nasal cavities, and vagina, rec tum and balanopreputial sac. On mucous membranes the disease begins with leukoplakia (q v) erythroplakia (q v) or a minute fissure having an infil trated base A fever blister of the lip which failed to heal is a common story Neoplastic leukoplakia bears the same relation to mucosal carcinoma as senile





Fig. 1627.—Squamous carcinoma: a small, dome-shaped, warty nodule with the usual central horny spike.

Fig. 1628.—Squamous carcinoma: the central spike has increased to a wide crust.

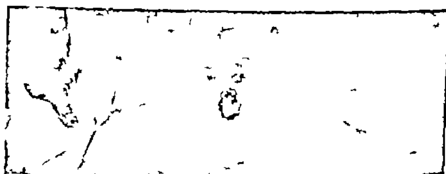


Fig. 1629.—Squamous carcinoma, classic.



Figs. 1630-1633.—Squamous carcinoma of ear and nose. Fig. 163[illegible], depicting a lesion deep in the concha, is quite unusual.



Figs. 1634-1636.—Squamous carcinomas of the dorsum of the hand, showing dome shape and central neoplastic keratinization.





Fig. 1637.—Squamous carcinoma of the hand.
Fig. 1638.—Squamous carcinoma on scar of burn.

keratoma to cutaneous carcinoma. Persons with oral carcinoma are as regularly of sun-sensitive complexion as persons with squamous carcinoma of the exposed skin.

Leukoplakia is white because the epithelium of which it is composed is excessively thick. If, instead of heaping up so as to cloud the visibility of underlying capillaries the abnormal epithelium exfoliates readily and forms only a thin covering for the mucosa, the clinical manifestation is a sharply marginated irregularly outlined area of raw beef appearance, described as



Fig. 1639.—Keratoses and large carcinoma of temple.





Fig. 1640.—Cancer has destroyed the upper two-thirds of the external ear.

Fig. 1641.—Advanced and huge, this vegetating carcinoma killed an old man. He might have died a better death if a small, early carcinoma had been recognized and treated correctly.

erythroplakia (q v) a form of early epidermal neoplasia. It tends to spread laterally and sooner or later ulcerates so that its carcinomatous nature becomes evident. In treating it the entirety of the neoplastic surface must be destroyed at once not piecemeal for if only a part is cauterized, the defect epithelizes in healing by proliferation of adjacent carcinomatous epithelium, and the result is worse than unsatisfactory. When carcinoma develops in

leukoplakia, the leukoplakia which surrounds the ulcer is composed of cancerous tissue. Sharply marginated, like the scaly keratosis found about many squamous carcinomas of the skin, such leukoplakia is the epidermal extension of the carcinoma. The leukoplakic margin, being part of the tumor must be destroyed. The intraepidermal spread of carcinoma about the main tumor mass is easily discerned on careful examination, and constitutes the reason for traditional wide excision, or the wide application of radiation therapy In





Fig. 1042.—Vegetative medullary carcinoma of neck.
Fig. 1043.—Vegetative squamous carcinoma of th penis.



Figs. 1044 and 1045.—Vegetating carcinoma. The tumor 1½ inch across, involved the skin of the thorax Section of it shows the conjunction of normal epithelium with abnormal. Recurrence did not follow wide surgical removal.

managing cancer of the lip recurrences will be prevented by destroying leukoplakia along with the ulcer and the size of the wound of extirpation can be kept minimum if the epidermal portion of the lesion is simply blistered off without destroying dermal tissue unnecessarily

Squamous Carcinoma Primary in the Nail Bed.—This was the rare diagnosis made by Levine and Lisa (ArchSurg 39 107 1939) in their case, and they collected records of 18 similar cases in the literature. Among these the low degree of malignancy was noteworthy Subungual verrucae (q v) are to be



Fig. 1646.—Carcinoma of the lip, shallow, with centrally bulging, granulomatous ulceration.





Fig. 1647.—Invasive carcinoma of the lip, which had already metastasized.
Fig. 1648.—Section of the lesion shown in Fig. 1647.







Figs. 1649-1651.—Carcinomas of the lip, not early. Fig. 1649 depicts the lesion in a full-blooded Negro, which is exceptional.

differentiated. Two cases were reported and 19 found in the literature by Bayer (ZntrblChir 74: 253 1949) In his patients, both elderly men, the first abnormality was a blue spot beneath the bed and this was followed by superficial ulceration. Russell (J 144 19 1950) in his review noted that a history of preceding trauma has been obtained in about half the cases. In the patient of Falk (WiseMJ 53 187 1954) the bone of the terminal phalanx was eroded which is rare The few cases I have seen developed in association with chronic x ray injury In treatment adequate surgical work is to be recommended see Mason (Surg 5 27 1939)



Fig. 1452.—Advanced carcinoma. (Dr Fred Harper)
Fig. 1453.—Advanced carcinoma of lip.
Fig. 1454.—Advanced carcinoma of buccal mucosa, with destruction of cheek.



Fig 1455.—Advanced carcinoma of lip
Fig. 1456.—Ulceration through skin and vegetation of metastasis in lymph nodes.

Mortality in the U.S.A. in 1932 1934 from cancer originating in the skin was approximately 2.6 per 100 000 roughly 3 000 deaths in each of those years (Sutton JKansMS 28: 97 1937) In 1949 there were 3,465 such deaths in the U.S.A. (Vital Statistics of the United States, 1949 FSA Govt. Print Off., 1951 p 460) The causes include melanoma, so that one may not say that every death was preventable but certainly a high proportion of them was.

In England and Wales, deaths from skin and lip cancer 1921 1923 ranged from 9.5 to 1.5 per 100,000 (Conrad and Hall: AmJCa 34 83 1930) The number who died per annum (excluding genital cases) was approximately 1,000 and the prevalence in males was about 70% over that in females (Ryle and Russell: BMJ I 875, 1947) It was the younger group of patients under 60 with skin and lip cancer who showed decreased life expectancy in the study of Peller (AmJMedSci 199 449 1940)

These figures do not suggest striking improvement in over all success of treatment, despite the facts that the cure rate approaches 97% and the hideous lesions common 30 years ago are seldom seen (Ed: BMJ 1: 956 1948)

Etiology—The essential cause of carcinoma is unknown. The role of chronic irritation, once considered paramount, is open to question and the part played by trauma is dubious. Spontaneous or induced by various agencies, the primary change seems to be one which affects the reproductive mechanism of the cell. Once altered, the cell is permanently different, and its progeny are similarly different from normal in appearance and behavior. The ability to grow where normal cells do not, invasiveness, speed of proliferation exceeding that of the normal epithelium, and inability to produce normally organized tissue structures are characteristics of carcinoma cells.

AGE, SEX, RACE.—The disease is usually one of adult life. Men are attacked 3 times more frequently than women (Broders J 74 656 1920). Carcinoma of the lower lip is a disease of males by a ratio of roughly 100 1.

In children the majority of the malignant lesions of the face are the result of xeroderma pigmentosum (q v) see Philipp (Ztschr.Krebsfor 5 126, 1907), 16 carcinomas; and Martin (JPediat 15: 163, 1939). In persons under 30 years of age Hall and Bagby (J 110: 703 1938) reported 60 cases affecting face and lip.





Fig. 1657.—Carcinoma of the tongue.
Fig. 1658.—Carcinoma of the penis, destroying the glans.

The white race is more susceptible than the Negro. In 1?6 skin ca cers occurring among 19 100 Negro patients, there w re 61 squamous of the skin 36 of the lip, 1 of the tongue 3 of the genitalia, 4 basal cell tumors, 1 sebaceous adenocarcinoma, 1 melanoma, a d 3 sarcomas of Kaposi according to Hazen and Freeman (ADS 62: 622, 1950). Among nati es of th Dutch East Indies Malay not Negro skin cancer of the face seemed not less frequent than among white people (TenSeldam: abs J 117 109 1941). See Etiology light

MECHANICAL, THERMAL, CICATRICIAL, CHEMICAL AND ACTINIC INFLUENCES are significant. Although the face and hands are the most common locations of squamous carcinoma ordinarily in a statistical study of 1 189 cases admitted to Kashmir Mission Hospital, Neve (BMJ 2 589 1910) found that more than 70% of the growths were located on the thighs and abdomen, because of friction heat and irritation from the use of portable fireboxes by the natives. The heated brick beds used in North China provoke similar lesions from repetitious burns of the thighs and hips of the natives (Kang cancer Laycock BMJ 1 982, 1948). Pipe smokers cancer and chimney sweeps cancer are recognized workers in tar and paraffin and farmers and sailors exposed to sun and

wind are frequent victims of the disease. Mule spinners cancer develops on the scrotums of cotton spinners in Great Britain, due to oils used in the lubrication of machinery

CHROMOSOMAL ALTERATIONS AND MUTATION THEORY —According to Boveri (Zur Frage der Entstehung Maligner Tumoren, Fisher 1914 transl, Williams & Wilkins, 1929) cancer tissue benign or malignant, can properly be defined as tissue composed of cells with nuclei wherein the numerical relations of the chromosomes have become distorted (see Metcalf J 84 1140 1925) While alterations in number have been proved not to be important in this connection, the genetic approach to the investigation is a productive one. Cohnheim s interpretation of tumors as representative of versprengte keime, which means sprung up embryos, has often been misquoted as suggesting an origin in embryonic rests (Harvey EdinMJ 65 1 1948)

An analogy exists between cancer a d homoiogenic induction in experimental embryology (Needham: BMJ 2: 892, 1936) Whatever it is that drives on the malignant cells to their uncontrolled growth resides within the cells (Cramer: BMJ 2: 997 1936) The organizer is a chemical substance of sterol sort related to carcinogenic and estrogenic substances disordered organization could, insofar as one now knows, be the chemical abnormality on which carcinogenesis depends (Needham: Order and Life Yale U Press, 1936)

The hypothesis has been pursued that the various known etiologic agents produce a gene alteration in a somatic cell, a mutation such that the progeny of the altered cell grow neoplastically Cancer in this light is not an infection or degenerati or an entity put upon one from without; it is a biologic phenomenon associated with somatic rather than germinal variatio spo t eous o ind ced, in cellular reproductive mechanisms (Sutton: ADS 37: 737 1938; 46: 1, 194.) See Burdette (CancRes 15 201 1955)

Among people with cutaneous cancer there is a somewhat higher incidence of c ncer of ther organs than should statistically be expected in a population without skin tum rs but otherwise similar (W rren and Gates: J 115 1705 1940)

See Pianese (BeitrpathAnat 20: Suppl 1, 1, 1896) abnormal mitoses; Stark (PhilHarperBiol 17: 51 1919) melanotic tumor appearing as mutation in Drosophila; Whitman (JCancRes 4: 181, 1919) review; Wilson (Genetics 9 342, 1924) tumors in Drosophila; Cockerell (Nature 118: 914 1926) mitotic error as possibl cause of tumors; Stadler (ProcNatAcadSci 14 69 1928) x ray mutations in maize; Patterson (Sci 68 41, 1928), x-ray mutations in Drosophila, noninheritance of somatic mutations; Muller (ProcNatAcadSci 14 714, 1928) x-ray and mutation Ledford (Ninth Scientific Report, Imperial Cancer Research Fund, London, 1930) review of chromosomal mechanisms in etiology of cancer; Lockhart Mummery (BMJ 1 785, 1932); Altenburg (Sci 78: 587 1933) mutations in Drosophila produced by ultraviolet; Cockayne (Inherited Abnormalities, Oxford U Press, 1933, p 28 ff.) mutation; Haldane (JPathBact 38 507 1934), review of Lockhart Mummery's "Origin of Cancer"; Sutton (J 104: 433 1935; SouthMJ 29 126, 1936); Jones (Sci 81: 75, 1935) chromosome-loss initiating pla t tumors Lockhart Mummery (BMJ 2: 1082, 1936); Dunning et al (AmJCanc 28 681 1936), heredity and somatic mutation in origin of malignancy; Jones (AmerN turalist 70 86, 1936); Wood (J 108: 1208, 1937); Lewis (PRMMC 12 280, 1937); McGowan (BMJ 1 698, 1938); Waddington (BMJ 1: 642, 1938) x ray mutation; Auerbach (ProcRoySocEdin 60 pt 2, 164 1940) Auerbach and Robson (ProcRoySocEdin 62 271, 1947) chemical substances producing mutations; Cowdry (J 133 408 1947) carcinogenesis; Symposium, Genetical Soc Great Britain (abs BMJ 2 36 1948) Fardon (Sci 117 441, 1953) somatic mutation; arguments against Fardon views by Blum (Sci 118 107 1953)

HEREDITARY FACTORS significant in the etiology of cancer of the skin include the inheritance of the xerotic, sun-sensitive type of skin which is predisposed to the development of keratoses. Epithelioma adenoides cysticum (q v) is often familial and may provide the lesions productive of basal cell carcinomas in several siblings. The genealogy of human beings is so mixed that inheritance is not interpretable as it is in animal experiments which have been extensive in the study of this problem.

See Slye (JCancRes 1: 479; 503, 1916; 2 213, 1917) inbred cancer-susceptible strain of animals Slye et al (JCancRes 2 401, 1917; 4: 207 1919) cancer-susceptible strain; Slye (JCancRes 6 139, 1921; 7: 107 1922), leukemia occurring only in cancer strain of mice; Sly (JCancRes 8 240, 1924) review recessive nature of spontaneous lesions Slye (JCancRes 10 15, 1926; J 86: 1599 1926), cancer-susceptibility Mendelian recessive, difficulties of statistical track, necessity for analytic, selecti breeding experiments; Slye (JCancRes 11 135, 1927 12 83, 1928) discussion of Little's work; Slye (AmJCanc 15 535, 1931), 116 000 autopsies of controlled stock of mice showing susceptibility beha ed as unit recessive, nonsusceptibility as a dominant; Cockayne (CancRev 2 337, 1927) the problem; Dill (BMJ 1 1217, 1930), heredity nd extrachromosomal influences McFarland and Meade (AmJMedSci 184 66, 1932) tumors in identical twins, extensive review; Warthin (JCancRes 9 279, 1925) human family with cance in 32% of 88 adult members; Hauser and Weller (AmJCanc 27 434, 1936) continuation of this study of Warthin; Martynova (AmJCanc 29 530, 1937) familial cancer of breast in human; Vandenberg (MichSMJ 49: 1183, 1950) breast cancer in mother 3 daughters and granddaughter

TRAUMA.—Cancer occasionally develops at the site of old injuries, especially in scars following burns, roentgen dermatitis (q v) lupus vulgaris

(q v) and lupus erythematosus (q v) and chronic ulcers may be the starting point. Irritation by tobacco contributes to the development of cancer of the lip and mouth (Friedell and Rosenthal J 116 2130 1941) see Leukoplakia.

Trauma as an initiating factor was discussed by Mack and Ellis (J 86 257 1926) and Leighton and Schmidtke (JMoMA 37 267, 1940) who reported 74 cases suggestive of a relationship and reviewed the literature. Single injuries are highly dubious as incitements to malignancy and have never succeeded experimentally (Davis AmJSurg 51 641 1941) Yet the problem is real especially when an industrial claim is made (Levin and Behrman IndMed M 10 519 1941) and patients persist in describing the injury which produced the lesion, putting 2 and 2 together and arriving at 7 I suspect. Acceptable criteria for the diagnosis of cancer arising from trauma were presented by Warren (AnnSurg 117 585 1943) It is imaginable that trauma might initiate intradermal growth of a superficial neoplasm (see pp 1183 and 1234)

SCARS were the site of origin of 13 cases of skin cancer reported by Iwamoto (abs ADS 14 197 1926) 9 of which were from burns 12 lesions were squamous, and 1 was basal cell. In America, Heidingsfeld (J 67 1499 1916) was among the first to call attention to the danger of malignancy arising in cicatricial tissue Arndt (BeitrKlinChir 157 305 1933) reviewed 100 cases only 3 of which developed before the age of 20 years. One appeared 67 years after the burn that caused the scar Cancer appeared only 5 months after a burn in the case of v Hasselbach (BeitrKlinChir 164 264 1936) The lapse of time from the burn until the appearance of carcinoma was inversely proportional to the age at the time of the burn, and the likelihood of development of carcinoma appeared considerably less if the area was grafted according to the studies of Lawrence (SGO 95 570 1952) Ulcers associated with osteomyelitis may be the starting point as in the 3 cases of Hobart and Miller (J 107 1116 1936) the neoplastic epithelium may invade the marrow spaces and necessitate amputation. Büngeler (MünchMWehn 81 1619 1934) reported an injury of the wrist dressed with a tar-containing tape beneath which cancer developed.

See Daniels and Friedman (AmJSurg 41, 304 1938), recurrence in center of pinch-grafted area, Cornil et al (Rassocfrancl étudecanc 28 359 1939), 15 cases; H [illegible] [illegible] (ADS 44 26, 1941) fatal case Lawrence (SGO 95 570 1952) 11 cases, plus 83 in literature, recommending early graft of severe burns for prophylaxis

X RAY AND RADIUM INJURIES may result in cancer see Burns, x-ray Dermatitis medicamentosa radium Carcinoma etiology mutation Basal cell carcinoma can result from radiodermatitis, but it has never been seen in radiodermatitis located on palms, soles or mucous membranes according to Anderson and Anderson (ADS 63 686 1951)

LIGHT —The influence of light has long been recognized in the causation of cancer of the skin (see Keratosis senilis, Xeroderma pigmentosum) Mathews (APath 23 399 1937) believed that the effect is not due to photodynamic sensitization The 14 patients of Büngeler (ZtschrKrebsfor 46 130 1937) with cancer of the face had hematoporphyrinuria which was not present in persons with cancers elsewhere and in his experiments, he found that sensitized mice developed more tumors from sunshine than mice not rendered more vulnerable by eosin porphyrin or tar *Büngeler traced the pathologic process* through stages of (1) inflammation (2) atrophy and beginning proliferation in the second month, with alopecia acanthosis, mast cell infiltration and progressive proliferation of the dermis; and (3) progressive development of tumors after the third month in continuity with the stage of proliferation.

Cancer of the skin has been induced in rats by experimentally subjecting them to ultraviolet energy (Holtz and Putschar MunchMWehn [illegible] 1414 1925; Ztsch Krebsfor 33 219 1931) The experiment of Roffo (Lancet 1: 472, 1936) on ultraviolet carcinogenesis in white mice have been instructive hyperkeratosis and cancerration followed a phase of local accumulation of cholesterol, which served, he thought, as a photodynamic sensitizer for he found that sensitivity to the sun varied with the blood cholesterol content at different times in the same individual. Beard et al. (AmJCanc 27: 257, 1936) also pro

duced cancer in mice with ultraviolet light. The lesions induced in the ear of the mouse appeared to be mainly fibrosarcomas (Grady et al.: JNatlCancInst : 209 1941) perhaps some were spindle cell carcinomas (q.v.)

That light acts on nuclei of cells in the same way as other forms of electromagnetic energy including x rays, the effect being degenerative was suggested by Blumenthal (ADS 33: 1042, 1936) The wave lengths involved in carcinogenesis are those under 3,200 A.U., according to Blum (JNatlCancInst 1: 397 1940) whose review indicated that knowledge of *the mechanisms involved is as yet hypothetical. Wave lengths must be longer than 2,537* A.U., for shorter ones are absorbed by the corneum (Blum and Lippincott: JNatlCancInst 3: 211, 1942) The minimum time required for induction of cancer by light cannot be reduced by intensifying exposure, but the time is reduced by giving the weekly total dose in small frequent exposures (Blum et al.: JNatlCancInst 3: 91 1942) The effect of ultraviolet light does not appear to depend upon its transforming skin surface fat into carcinogenic substances (Knapp et al. CancRes 10: 73, 1950)

The interrelations of sunshine complexion and heredity were studied by Hall (ADS 61: 589 1950) who concluded that sunlight is an important factor in certain stocks of human beings but not in others, such as the Negro. Sun bathing has been variously assessed as healthful or hazardous because of the dangers of skin cancer The experienced clinician is not hesitant in telling a particular patient whether sun worship will or will not be dangerous for him. A fad can justifiably be censured simply because it is a fad, and, since time appears to me to be valuable I wonder whether some people might be able to use their hours to greater advantage. The tumors affecting skins capable of tanning are more often basal cell, while those affecting nontanning skins tend to be squamous (Taussig and *Williams: APath 30: 721 1940)*

There is no proof that indiscriminate use of ultraviolet lamps is harmful (Coblentz: J 136: 1040, 1948) yet the ill effect in some individuals of prolonged, intense exposure to sunshine is apparent to any physician whose practice includes outdoor people of older age groups (Piers: BJD 60: 319 1948) A man given a prolonged course of mercury vapor lamp treatments on the chest and back developed typical sailors skin on the treated areas a year after the last treatment (Colquhoun: BJD 39: 346, 1927) In 190 cases of cancer of the skin seen in 900,000 cattle slaughtered in New South Wales, all but 3 began upon white areas, and those 3 developed in the scars of brands (Drabble, quoted by Findlay: Lancet 1 1229 1930)

The incidence of carcinoma of the lower lip exceeds that of the upper apparently *because of the amount of solar radiation it receives (Molesworth DWchs 99: 1134 1934)*

OCCUPATIONAL CANCER occurs in sun-sensitive skins much exposed to sun light (Phillips TexasSJM 36 613 1941) in workers with tar and pitch in workers exposed to absorption of arsenic, and in mule spinners (Brockbank BMJ 1: 622 1941) Occupational cancer due to pitch and tar was discussed and well illustrated by Ross (BMJ 2 369 1948) Carcinogens and suspicious chemicals have been isolated from rubber (Falk et al. CancRes 11 318, 1951) Occupational cancer is rare and the etiologic relation of the work is hard to prove (Eckardt SouthMJ 47 62, 1954)

See Ross (JCancRes 3: 321, 1918) coal, tar pitch, soot, oil fractions, dyes, petroleum workers, handlers of radium and x rays; Bridge and Henry (Industrial Cancers, Wright & Sons, 1928); Shambaugh (J 104 2326, 1935) tar cancer of lip in fishermen; Somerford (BMJ 1 1304, 1936) occupational tar cancer; Gehrmann (J 107 1437 1936), occupational materials and chemicals, including dyes Prunes (also ADS 46 290 1942) Chilean nitrate workers Henry (Cancer of the Scrotum in Relation to Occupation, Oxford U. Press, 1946); Hueper (J 131 736, 1946) control; Schwartz et al (Occupational Diseases of the Skin, Lea & Febiger 1947, p 667 ff) brief but complete with bibliography; Cruickshank and Squire (BritJIndustM 7: 1 1950) from oils in engineering processes; Downing (J 148 245, 1952), compensation problems Currie (Practit 238 400, 1952) occupational hazards Combes (Coal Tar and Cutaneous Carcinogenesis in Industry Thomas, 1954); Macdonald (J 157: 5, 1955) classification of carcinogenic industrial hazards.

NUTRITION *in relation to growth of cancer has* received consideration tumors grow better in animals which are well fed, and the incidence of neoplasia appears to be diminished in animals suffering deficiency in diet (Voegtlin and Thompson PublHRpts 51 1429; 1689 1936) Underfeeding not only had an inhibitory effect on tumor formation, but induced cancer appeared later and was partially inhibited in underfed mice (Tannenbaum AmJCanc 38 335 1940 Edit J 129: 1169 1945; Boutwell et al.: CancRes 9 747 1949) Vitamin A metabolism may be concerned (Popper and Ragins APath 32: 258 1941) The respiration of the epithelium of early cancer was different from, and generally less than, that of normal epithelium (Amersbach et al. ADS 46 269 1942) See Precancerosis Kraurosis; Dysphagia and xerostomia in women.

ARSENICAL CARCINOMA.—Arsenic as a cause of carcinoma was recognized by Hutchinson (TransPathSocLond 39 352, 1888) in 6 cases of psoriasis treated with arsenic with resultant neoplasia. About one-third of arsenical cancers are basal cell in structure, although most are squamous. Metastasis may occur despite the apparent low grade of the tumor. Inorganic arsenic is far more dangerous than organic. Arsenical keratoses, typically involving the volar surfaces, may become cancerous or may undergo involution, particularly if the ingestion of the drug is stopped.

Multiple, superficial basal cell epitheliomas of the trunk are usually arsenical in origin, the arsenic having been absorbed perhaps 20 years prior to the appearance of cancer. Leitch and Kennaway (BMJ 2 1107 1922) fed rats and mice potassium arsenite but obtained no carcinogenesis in a short time; however, by applying it to the skins directly they evoked tumors which metastasized. Fransecn and Taylor (AmJCanc 20 287 1934) felt that in cases of multiple carcinoma of the skin there is no justification in incriminating arsenic unless it is microchemically demonstrable in the lesions or unless typical keratoses are present on the volar surfaces (see Dermatitis medicamentosa, arsenic). This view is debatable.

Montgomery (ADS 32: 218 1935) studied the differences between arsenical lesions and superficial epitheliomatosis and Bowen's carcinoma; he found that some persons with typical arsenical lesions show no demonstrable arsenic in their skins, but as a rule the element is present in pathologic amounts, and more of it is in the epitheliomas than in the adjacent skin, for the reason, I suggest, that there is simply more epithelium in a lesion than in the adjacent skin. Carcinoma, he stated, developed in about 20% of the keratoses, which are "carcinomas in situ," and pigmentation was present in half the patients. Keratoses appeared as early as 1 month and as late as 30 years after the first ingestion of the chemical. The average time interval from exposure until cancer appeared was 18 years in the study of Neubauer (BritJCanc 1: 192, 1947). Three times as many men as women were affected.

Occupation is an important factor in etiology (Ullmann: DWchn 97: 1019, 1000; Hueper: SouthMJ 43 118 1950), and workmen exposed to absorption of arsenic must be especially carefully protected. Farmers are exposed to sprays. Masks, generous ventilation, the washing of the hands before eating, and changes of clothing are among the preventive measures applicable. The wise choice of medicines on the part of practitioners who should have a desire to stop them as well as to start them, will likewise go a long way, for Fowler's solution is a dangerous drug (Arbelger and Kremen: Surg 30: 977 1951).

See Goeckerman and Wilhelm (ADS 42 841, 1940): arsenical carcinoma of ureter and bladder; Montgomery and Waisman (JID 4: 365, 1941): arsenic generally not demonstrable in superficial epitheliomatosis; Arguello et al. (RevArgentDermat 26 313, 1942): endemic arsenical disease; Hueper (CancRes 2 551 1942): in rats; Frank (ActaD-V 20: 161, 1939); case Sommers and McManus (Canc 6 347 1953): 27 cases, 19 males, 13 treated for psoriasis with Fowler's solution, 4 autopsies: other organs involved included bladder, prostate, esophagus, lung, breast, pancreas, colon, kidney.

EXPERIMENTAL CHEMICAL INDUCTION of cancer was begun when Yamagiwa and Ichikawa (JCancRes 3 1 1917) showed that the repeated application of tar to a rabbit's ear will provoke warty growths, some of which become malignant. Many investigators have pressed the advantage of the valuable knowledge that cancer can be provoked experimentally, and researches with pure chemical substances, particularly the benzopyrene derivatives, are continually fruitful. Cook and Kennaway were able to obtain chemically pure carcinogenic hydrocarbons, and their work greatly advanced investigations in this promising direction (Cook et al. AmJCanc 29 219 1937; 33 50, 1938; 39 381 428 521 1940). See Wolf (Chemical Induction of Cancer, Harvard U Press 1952).

The carcinogenic action having been exerted and cancer initiated, no further part is played by the chemical agent (Guy: BMJ 1 591, 1938).

Smegma is of interest as a carcinogen, for circumcised males do not develop cancer of the penis; the carcinogenicity of smegma is shared by other fatty substances of biologic origin (Edit: BMJ 1: 987 1943). See Penis, carcinoma of (p. 1204).

Early epilation is a striking feature of carcinogenesis with some hydrocarbons, but not with others, reported Orr (JPathBact 46: 495 1938). Hair which regenerates after carcinogenic epilation is abnormal. Squamous hyperplasia of the epidermis is produced in the first weeks, and thereafter the progressive changes appear at a level, particularly the first superficial, deeper tissues. Collagen is transformed into fine fibers lacking in refractility.

ficially later throughout the skin. Passive congestion of the subcutis, alteration of texture of the elastic tissue and absence of inflammatory cellular reaction are further notable features.

Mice receiving cortisone developed more carcinomas than controls when painted with methylcholanthrene (Piccagli et al.: JID 22: 317 1954)

Monographic is the article by Furth (AnnRevPhysiol 6: 25, 1944) "The carcinoma cell constitutes a new cell type in a given host with a varying degree of deviation from normal and limitation of freedom from forces controlling normal growth." The bibliography simplifies access to pertinent literature. It suffices to quote Gye (BMJ 2 1276, 1936) who wrote: "It is now known that cancer begins as a change in a single normal cell or small group of normal cells, which acquire the power of autonomous growth. The factors which confer on a cell the property of autonomous growth reside within it and cannot be attributed to agents acting from without, though these may be a remote cause. He (BMJ 1: 551 1938) pointed out that there are two sorts of causes, those leading to the occurrence of the tumor and those which explain the properties of the malignant cell the agent responsible for the start plays no further part in the progress of th lesion after the malignancy has occurred, so the tumor can then be propagated interminably in th experimental animal without further action of the carcinogenic agent. An agent which, when applied to epithelium incites carcinoma, will, when applied to connective tissue incite sarcoma.

Tumors induced by tarring the skins of rabbits were of especial interest to Foulds (CancRes 14 327 1934) who noted that, while warts develop early some regress during the period of tarring, while all regress if tar is withheld, showing that these warts are "conditional tumors" dependent upon extraneous stimulation. Tumors which have regressed during intermissions of tarring recur however if tarring is resumed. There is thus suggested the existence of separate elements in carcinogenesis: tumor inception, and tumor promotion. Initiating agents convert normal cells into "latent tumor cells," an irreversible state, demonstrable 6 months after withdrawal of tar. Promotion, however is reversible promoting agents possessing the effect, it seems, of producing conditions favorable to cell proliferation in general. Initiation may be a process rather than an event.

CHEMICALS, VARIOUS.—See Bullock and Rohdenburg (JCancRes 3 227 1918) Scharlach R; Evans (JUrol 38 212, 1937) 13 cases benzidine, beta-naphthylamine and other nitro and amine dyes causative of cancer of bladder; Shear (AmJCanc 29 269 1937) azo compounds and cancer of liver in mice; Ferguson (JUrol 38: 242, 1937) aniline dyes and bladder cancer Hueper (APath 25 856, 1938) aniline bladder tumors, bibliography Mayer (JID 10 389 1948) amines and azo dyes, review of chemical carcinogenesis; Rosen and Hachmilewitz (CancRes 14 494, 1954) rats on thiouracil developed squamous carcinoma of the ? ca.

TAR.—See O'Donovan (BJD 32 215; 245, 1920) small lesions induced by tar cancerous from the onset Gretz (ZtschKrebsfor 21: 415, 1924) early lesions; Bittmann (ZtschKrebsfor 22 276, 1925) tarring of rabbits' ears; Harmblase (1927 quoted by Craver, J 105 1820, 1935) bladder cancer in psoriatics treated with tar, Watson (JPathBact 34 201 1931) squamous carcinoma of white rat produced by tar; McIntosh (BritJExperPath 14 422, 1933) fowl sarcoma from injections of ta ; Mottram (AmJCanc 22: 801, 1934) tar cancer malignancy related to growth rate; Mottram (JPathBact 40 407 1935) latent period between tar application and cancer development; Twort and Twort (JPathBact 42 303, 1936) tar cancer in mice Reinhard and Candee (AmJCanc 26: 382, 1936) skin tumors resulting from feeding tar; Flory (ProcInstMChi 13: 265, 1941) tobacco tar carcinogenesis in rabbit; MacKenzie and Rous (JExperM 73 365, 391, 1941) partial tarring inadequate to produce cancer makes subsequent tar carcinogenesis quicker epithelium of tar wart if allowed to cover a skin loss is abnormal epithelium.

CIGARETTE TAR condensate applied to the backs of mice, in a dose of 40 mg. of tar in acetone 3 times a week, produced cancer in 59 of 81 mice after 32 weeks, which is about half a lifetime, analogous to the 20 to 25 years of smoking a human being requires to get lung cancer reported Wynder et al. (CancRes 13 855, 1953); Wynder et al. (CancRes 15, 445, 1955) condensed cigarette smoke carcinogenic in Swiss mice.

HYDROCARBONS.—See Kennaway (BiochemJ 24 497 1930) dibenzanthracene; Cook et al (ProcRoySocLond 111 485, 1932) production of cancer by pure hydrocarbons; Fieser and Seligman (JAmerChemSoc 58 2482, 1936), synthesis Shear (AmJCanc 26: 322, 1936), cholanthrene Andervont (PHR 11 812, 1936) 46 chemical carcinogens known to date Barry et al. (ProcRoySocLond B 123 343, 1937) pure compounds Mottram (AmJCanc 32 76, 1938) radium and benzpyrene cause cancer with less of hydrocarbon than when it is used alone; Maurer (ArchExpZellfor 21: 191, 1938) hydrocarbon effects on tissue culture, Cottini and Mazzone (AmJCanc 37: 186, 1939), benzpyrene effects on man; Pullinger (JPathBact 50: 463, 1940), early changes induced in epidermal cells by benzpyrene and methylcholanthrene; Creech (AmJCanc 39 149 1940) chromosomal effects, Hartwell (Survey of Compounds Which Have Been Tested For Carcinogenic Activity USPHS, 1941), 371 page bibliography Mottram (BritJExperPath 26 1, 1945) the change from benign to malignant, Rous and Smith (JExperM 81 597 621, 1945) induction of neoplasia in embryo skin; Boyland and Horning (BritJ Canc 1 118, 1949) nitrogen mustard; Ma (CancRes 9 481, 1949) dermal changes during epidermal carcinogenesis Carruthers (CancRes 10: 255, 1950), chemical changes in epidermis during carcinogenesis; Shubik (CancRes 10 241 713, 1950), different methods of chemical carcinogenesis Rees and Rogers (CancRes 10 226, 1950) methylcholanthrene followed by Shope virus Gerver et al. (CancRes 11: 474, 1951) intravenous carcinogen caused skin cancer in rats, Survey of Compounds Which Have Been Tested For Carcinogenic Activity (USPHS, 1951) 1,329 simple compounds, omitting complex mixtures; Wolf (Chemical Induction of Cancer Harvard U Press, 1952) 250 pp., review; Davibhadhana (CancRes 12 168, 1952) epidermal cell changes Montagna et al. (JID 22 329 1954) histologic changes following methylcholanthrene applications on hairless mice, results t growths consisting of aggregated hyperplastic sebaceous adenomas; Piccagli et al. (abs YBD 1954, p. 403) effect of interval between applications of methylcholanthrene on albino mice frequent repetition shortened latent period, no desensitization or suggestion of pertinence of allergy; Rigdon and Brashear (CancRes 14 428, 1954) methylcholanthrene on chickens incited lesions simulating squamous carcinoma but regressing spontaneously in a few weeks.

ESTROGENIC HORMONES and carcinogenic derivatives of tar are related chemically and the carcinogenic properties of estrogenic substances have been investigated. Huge doses apparently promote cancer in susceptible mice the ill effect of therapeutically valuable doses in human beings is probably nil

See Loeb (J 104: 1597, 1935), Graver (J 105 1820 1935) Cramer and Horning (Lancet 1 247 1939); Gardner (APath 27: 138 1939) bibliography; Allen (J 111: 2291, 1940) Morton (SGO 72 346, 1941) review

PARASITES.—The carcinogenic properties of Cysticercus infestation (Bullock and Curtis ProcNYPathSoc 1920 p 149) and of Spiroptera infection (Fibiger ZtschKrebsfor 13 217 1913 14 295 1914) require mention. *Cysticercus fasciolaris* larva of the cat tapeworm often provokes malignancy the tumors appearing in parasitized rats in increasing incidence after 8 months until 20 months of parasitism (Curtis et al. Sci 77 175 1933) When cancer begins it does so first in only a small area of 1 cyst, and the more cysts the host carries, the more likely he is to suffer malignancy In 5 of 8 cases of primary cancer of the liver seen in Bahia, *Schistosoma mansoni* was present and appeared to have an etiologic relationship (abs J 117 1049 1941) Mahmoud Ahmed Afifi wrote an interesting essay (Bilharzial Cancer Lewis, 1948) on the relation of the Egyptian worm and cancer of the bladder prostate and colon See Dunning and Curtis (CancRes 13 838 1953) regarding the carcinogenic effects of larval extracts under some circumstances.

Viruses are known to cause carcinoma The rabbit papilloma (Shope JExperM 58 607 1933) otherwise resembling condyloma acuminatum often becomes malignant. Cancerous rabbit papillomas with metastases were described by Rous and Beard (PSExperBiol 32 3o8 578 1935) and cancer may appear within 2 weeks rather than in from 4 to 8 months if the warty lesions are tarred When tar is first applied and the virus is inoculated into the tar warts, cancer appears quickly (Rous and Kidd Sci 1936, p. 468); the virus produces this same effect if it is introduced by injection into the blood (JExperM 67 399 1938)

Rabbit papillomas induced by Shope virus can be cured by doses of x ray therapy which do not destroy the virus (Friedewald and Anderson JExperM 78 ..., 1943). Cultures of Rous's sarcoma may be dosed with irradiation so that no living cell survives and then the cell-free material induces cancerous change in a culture of fibroblasts (Ed BMJ 1: 1090 1939) Gye (BMJ 1: 511 1949) thought that transmission of mouse tumors by means of dried refrigerated, presumably cell free material argued for virus etiology but Passey and Dmochowski (BMJ 2: 11..; 1134; 1136 1950) proved that the cells were not dead and believed that the tumors so transmitted were in fact transplanted. Shope papillomas and Rous sarcomas differ from other tumors in being capable of heterotransplantation from the time of their inception (Greene: CancRes 13: 726, 1953)

Viruses act only as other carcinogens do according to Murphy (PSMMC 11: ... 1936) Whether viruses cause all cancer was discussed by Rous (AmJCanc ..: 2..., 1936) see Edit (J 109 394 1937) Kidd (BullJHH 8..: 583 1948) reviewed the literature on virus and viral agents in relation to cancer See Gregory (SouthMJ 43: 1 ... 1950) and Andrewes (BMJ 1: 81 1950)

Great difficulties in accounting for all facts are faced by the proponents of viral genetic or any other single explanation. What knowledge is to be added in future years cannot be guessed it is exciting and of absorbing interest as it unfolds.

Pathology—In squamous carcinomas proliferative epithelial projections extend into the connective tissue and round, pearly masses, made up of cornified epidermal cells are formed in the carcinomatous tissue both locally and in the lymph node metastases. The growth spreads out like the roots of a tree and a single cross section may show groups of isolated cells and pearly masses which followed three-dimensionally prove to be connected with the rest of the growth The pearls are groups of cells arranged concentrically and presenting changes progressively from the periphery toward the center corresponding to the changes in the normal epidermis from the deep layers to the surface Keratinization is irregular and parakeratotic.

In gross outline, almost all small cancers are circular or would be if the skin were not under tension, which can make them oval. With progression, the neoplastic tissue grows where circumstances are favorable, so that, as shown by Mohs and Lathrop (ADS 66 427 1952) irregularities of shape re sult from outgrowth following fascial planes periosteum, vessels and nerves. In this respect it seems to me basal cell tumors are less predictable than squamous in their advanced stages. The fact argues in favor of microscopic control of any effort to eliminate cancerous tissue from its host.



Fig 1659 —Gross section of squamous carcinoma, 3 cm. in diameter widely excised so as to amputat all primary tumor tissue. Knowledge of whole-tumor architecture is essential to intelligent treatment. (Stout Human Cancer Lea & Febiger 1932)





Fig. 1660 —Squamous carcinoma. Infiltration by narrow strands, and horny degeneration of all but peripheral cells of every aggregate more than 3 or 4 cells thick.

Fig 1661 —Squamous carcinoma. Normal epiderm is seen at lower right, with sharp hange in cell type t edge of cancerous proliferation. Cancer cells fill the dermis and under mine the edge of normal epidermis.

To distinguish histologically between pseudoepitheliomatous hyperplasia at the edge of an ulcer and the development of carcinoma may be not merely difficult but actually impossible (Winer: ADS 42 856 1940) Infiltration must extend into the level of the sweat glands if one is to be comparatively sure. Clinical behavior not morphologic histology is the final criterion.

Eosinophilic massive cell infiltration was remarkable in the neck nodes of a young man with a chin primary but metastatic carcinoma was not present in this unusual granuloma reported by Andrews (ADS 69 120 1954)



Fig 1662.—Squamous carcinoma. The cells of the infiltrating strands undergo cornification, and the whole surface is covered with tumor tissue, which likewise contains in retention of nuclei, manifesting parakeratosis. Typical inflammatory stroma.

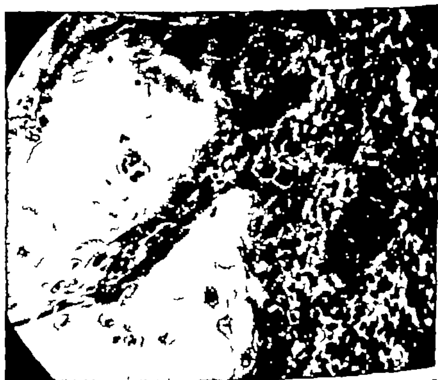


Fig. 1663 —Squamous carcinoma, showing keratinization of internally located cancer cells and prickle cell in action of the inflammatory stroma.

CULTIVATION of cancer tissue in vitro has long interested investigators. Dalos (AmJCanc 26 5?1 1936) found it difficult to grow squamous carcinoma because of microbic contamination while other human tumors he (AmJCanc 29: ?, 193?) grew more successfully the spontaneous human malignancy contains, he thought, ...

and labile material. Mammalian carcinomas have been grown in the yolk sac of the chick embryo and a technic elaborated by Taylor et al. (Sci 96: 343, 1942) was almost 100% effectual in the cultivation of mouse carcinoma tissue.

TRANSPLANTATION of tumor tissue was demonstrated in 1900 by Jensen and Loeb, according to Wood (J 84: 4, 1925) who called attention to the significance of this with respect to technic of biopsy and treatment. Autoinoculation experiments, grafting human skin tumors into normal sites, were performed by Crosti (GiorItalD 77: 145, 1936), but the lesions eventually stopped growing and lost their malignancy. Flarer (GiorItalD 78: 396 1937) successfully accomplished autotransplantation. Basal cell tumors were later successfully transplanted by Crosti (GiorItalD 79 1091, 1938). There is no doubt that cancer may be transplanted in the course of surgical work both from manipulative translocation of viable cells and from their conveyance by the blade of the scalpel. See Metastatic tumors in the skin experimental (p. 1310)

EXPERIMENTAL TRANSMISSION of cancer in animals depends on the transplantation of viable cell (Krotkina: AmJCanc 33: .53, 1938). The serial passage of a tumor is possible only in the species in which it arises and is usually restricted to animals of the same genetic strain, st ted Craigie (BMJ 2: 1485, 1949). It depends on inoculation of living tumor cells, which, since they retain genetic characteristics of the original host are rejected by a genetically alien one. The exceptions are few but include the carcinogenic viruses, which produce tumors de novo by infecting the cells of the host. After inoculation of a host with a suspension of tumor cells the transplanted nodules ppear suddenly at various times after the inoculation, and when first recognized the transplanted tumor is generally at least 1 or 2 mm in diameter. Its sudden appearance is puzzling (cf. p. 1311)

HETEROTRANSPLANTATION of various malignant tumors from the host to the anterior chamber of the guinea pig eye has been accomplished by Greene and Saxon (JExperM 67: 691 1938); see Greene (Sci 88 357 1938); Greene and Lund (CancRes 4: 35., 1944). The manner of growth of a frog carcinoma transplanted to the eye of a mammal was interestingly described by Lucké and Schlumberger (JExpe M 70: 257 1939). Early tumors cannot be transferred to normal animals, but tumors obtained after metastasis are often transplantable (Greene CancRes 11: 899 1951). The tumor acquires its ability to survive in the environment of the normal animal, an ability which it does not possess at the time of its inception.

THE STRUCTURE AND CLINICAL BEHAVIOR of most individual, transplanted tumor strains remain remarkably constant over long periods of time (Foulds AmJCanc 39: 1, 1940). Some tumors ha e been maintained by serial transplant tion for more than 30 years without subst ntial change. Constancy of structure and of behavior is, however not invariable in transplanted tumors. Strong (JCancRes 10: 219 1926) and others have described sudden irreversible changes, which they term "mutations, during th transplantation of mouse tumors. The form and arrangement of cells are modified by mechanical factors such as mutual compression or lack of support.

In histogenetic classifications it is assumed, probably correctly that the differentiations in tumors are limited to those which the parent tissue can manifest. It is probable that all the possible differentiations of a tissue can be revealed in the various tumors to which it gives origi but some differentiations are common and others rare and the majority of tumors derived from a si gle tissue can be classified in a few fairly well defined groups.

Experimental investigations of tumors allow the following deductions, Foulds con tinued (1) Tumors, with rare exceptions, retain permane tly those genetic properties which disti guish the tissues of one animal species from those of all other species; (2) t mors retain in great measure at least, the genetic specificity of the individual in which they originat ; (3) tum rs retain to a variable extent the properties of the particular tissue from which they riginat ; (4) each tumor has specific properties, so that tumors owning the same parent tissue have family resemblances but individual peculiarities; (5) ll these properties are permanent and hereditary; and (6) the process of conversion of normal into tumor cells is irreversible.

Tumors arise Foulds continued, from adult cells and th ir structure and behavior are determined by anaplasia, not by "embryonal qualities. Embryonal normal cells do not behave a cancer cells. Attempts to discove fundamental diff rences between normal and cancerous cells of the same type wrote Cowdry (APath 30: 1 45 1940) have failed t bring out any striking variation in chemical make-up nzyme content, metabolism or structure Differences re qualitative. Neither normal n r cancerous cells are uniform in properties. H stated that both go through periods of youthful vigor maturity and old age ending in death. To compare young epidermal cells capable of multiplication, with keratinizing cells in a squamous cell carcinoma would be misleading. Selection of correspondi g periods in the life cycles of both is difficult, but it should be attempted. Malignant cells are seldom uniform in their properties throughout a tumor. The cells in some areas may be proliferating rapidly while those in others may be undergoing varieties of degeneration.

Both malignant and normal cells may die quickly o slowly. Tumor cells suffer the same degenerative changes as normal tissue. Cells of normal tissues may die in orde ly strata, as in the epidermis in consequence of progressively increasing deprivation of vital

necessities. Some *epithelial cells* discharge their allotted function by dying in the right way—they keratinize. Malignant cells of the *same lineage* may also keratinize though perhaps not in quite the same fashion.

The *cell* is the unit of cancerous tissue as of normal tissue Strong observed. He pointed out that inoculation of cancerous tissue is transplantation and not infection and that uniform behavior of a tumor implies a relatively stable mechanism for its perpetuation.

Estimation of Malignancy (Grading).—Squamous carcinomas were separated by Broders on histologic examination into 4 grades dependent on the relative proportions *of differentiated'* and undifferentiated cells, Grade I being least malignant *and Grade IV* most malignant (Math 2 376 1926 TexasSJM 29 520 1933)

He found good *correlation* between his pathologic grade and the actual result in the case *so that grading* seemed to be of prognostic importance. While the service so rendered may be of aid to surgeons unfamiliar with microscopic *architecture* I believe that what Broders called differentiation is in fact *degeneration* and that the outcome in a given case depends on the removal or *incapacitation of all* cancer cells whatever grade they may be assigned *to* and that such removal is easy in small lesions and difficult in advanced ones, *without* regard to the grade and that in carcinomas in which the cells proliferate with little tendency to adhere to each other the removal *of all of them* is on that account rendered difficult for they diffuse through the *tissues* and metastasize readily as compared with tumors in which cells *tend to cohere* and to form well-developed horny pearls and finally that the *business* of grading is permeated with subjectivity while it loses sight of the *fact that **a tumor is as malignant as its most malignant part*** a part which may elude the examiner

Invasiveness of epithelioma clearly bears some relation to the physical *properties* of the cells (Sutton ADS 46 1 1942) If they do not stick together *they* can more readily insinuate themselves between normal tissue elements *and* can more readily reach lymph nodes. If they do stick together they *are likely* to remain shallow for a long time and daughter cells are lost by keratinization scaling off the surface rather than producing viable progeny in a favorable environment wastage by keratinization' (Mottram AmJCanc 22 801 1934 JPathBact 40 407 1935)

The faster the rate of growth, the sooner downgrowth will occur It is clinically true of early cutaneous carcinoma that the wider the surface extension before dermal invasion takes place the more benign the lesion. The growth of a colony of altered cells may be practically without coherence (Sutton ADS 37 737 1938) If slow growing the cells permeate the epidermis as in Bowen s disease of the skin. If swiftly-growing the clumps of cells expand *within* the epidermis and soon burst through the normal confines, requiring only a short time to become obvious cancer Cells of weak cohesion spread into the dermis in isolated units and clumps of small numbers. These correspond to Broders most malignant class. They should be—and in fact they are—the most malignant as judged by their readiness to metastasize The rate of ulceration, studied by Wilson (ADS 41 667 1940) was reported to vary with Broders grading of the tumor the lesions of low grade ulcerating slowly and those of higher grades ulcerating rapidly except tumors of *Grade IV* which ulcerate slowly because they invade fast

Cohesion of cancer cells was studied by micromanipulation method by Coman (CancRes 4 625 1944), who found marked differences from the normal in the ease with which cancer cells could be separated from one another The diminution of adhesiveness might be concerned with the low calcium content of squamous carcinoma tissue (Coman Sci 100 347 1944)

Epithelium is a tissue which has a conspicuous biologic attribute possesses the property of covering surfaces on which it is capable of growing When the surface has been covered, continuation of growth results in stratification folding and secretion of distal cells. If an alteration of epithelium resulted in its possession of the property of

provoking granulation tissue in which it could grow of provoking mesodermal supportive tissue which served as a habitable surface however folded, then the growth of this new species of epithelium would constitute a carcinoma.

Classification and Prognostic Interpretation of epitheliomas of the skin may be devised to take into account the properties of cohesiveness and of rate of growth, the necessary information being provided, respectively by microscopic examination of tissues and by clinical observation of lesions. Other factors influence accurate prediction: (1) the stage of advancement of a tumor (2) the location and accessibility of its growth, (3) the presence or absence of metastases, which in effect merely complicate the mechanics of its removal in the entirety (4) the histologic evidences of totality of removal when attempted and (5) the factor inevitably involving personalities—who treats the patient—for experiences are particulate and involve human beings.

Correlation of Clinical and Histologic Features of Epidermal Neoplasms

Coherence (Histologic Estimation)	Rate of Growth (Clinical Estimation)		
	A (Slow)	B (Moderate)	C (Fast)
I (strong): Progress by spread at dermo-epidermal junction as stratified band, which warps and folds	Quiescent warty keratoses Quiescent thick leukoplakias Cutaneous horns Slowly progressive vegetative, stratified squamous cell epitheliomas containing large pearls with thick epithelial borders Most basal cell epitheliomas	Progressive warty keratoses Progressive thick leukoplakias Vegetative squamous cell epitheliomas with well-developed pearls showing stratified epithelial borders Transitional cell epitheliomas with stratified epithelial structure Some basal cell epitheliomas	Rapidly progressive warty keratoses Rapidly progressive thick leukoplakias Vegetative and ulcerative epitheliomas with well-developed pearls showing stratified squamous epithelial structure, generally slow to metastasize Some transitional cell epitheliomas Some basal cell epitheliomas
II (moderate): Progress by spread at dermo-epidermal junction as sheet of single-cell thickness, folding, supplanting and engulfing	Quiescent scaly keratoses Quiescent scaly leukoplakias Squamous cell epitheliomas containing pearls with thin epithelial borders	Progressive scaly keratoses Progressive thin leukoplakias Vegetative and/or ulcerative squamous cell epitheliomas containing pearls with thin epithelial borders	Rapidly progressive keratoses with thin scales, bleeding readily Rapidly progressive erythroplakias Ulcerative epitheliomas containing pearls with thin epithelial borders, metastasizing readily
III (weak): Progress by intraepithelial becoming intramucosa, infiltration of single cells and small groups of cell cornification of single cells and small groups giving "anaplastic" appearance	Inactive scaly keratoses which bleed readily Inactive flaking leukoplakia and erythroplakias Quiescent intraepidermal Bowen's and Paget diseases	Progressive keratoses with thin scales, bleeding readily Progressive erythroplakias Early and late lesion of Bowen's and Paget diseases Ulcerative epitheliomas with cornification of single cells and small groups of cells	Rapidly progressive Bowen's type of keratoses becoming infiltrative cancers Rapidly progressive Bowen's and Paget's diseases Early nodular infiltrative, intracutaneous, "anaplastic" cancers Ulcerative infiltrative, epitheliomas with cornification of single cells and small groups of cells, metastasizing readily

Four Basic Structural Forms of Early Skin Cancer exist

(1) Subepidermal Spread in Stratified Sheets of More Than Single Cell Thickness which replace normal epidermis and warp and fold to form warty keratoses and pearl-containing downbuddings and insinuate themselves along the dermo-epidermal junction so as to undermine supplant and engulf epidermis and accessory structures. This form represents strong cohesion, and clinical examples are warty keratoses, leukoplakias and usually vegetative epitheliomas of relatively low malignancy

(2) Subepidermal Spread in Sheets of Single-Cell Thickness which fold to form the earliest downbuddings and insinuate themselves along the

dermo-epidermal junction (line of least resistance) so as to undermine supplant and engulf epidermis and accessory structures. This form represents moderate cohesion, and clinical examples are scaling keratoses erythroplakias and ulcerative epitheliomas of considerable malignancy

(3) Subepidermal Spread in Single Cells and Small Groups of Cells. This form represents weak cohesion and appears clinically as a minute intracutaneous nodule from the center of which may extend a tiny horny spike. Within when noncohesive growth is speedy anaplastic,' invasive and highly malignant growth results while necrobiotic cornification of single cells and small groups of cells generally occurs.

(4) Intraepithelial Spread in Single Cells and Small Groups of Cells. This, like the third form, represents weak cohesion and appears clinically as senile keratosis Bowen s disease or Paget s disease which are varieties of keratinizing epithelioma, usually but not always, rapid in growth rate.

See Virchow (AfPathAnat 1 94 1847) Thiersch (Der Epithelialkrebs namentlich der Haut, Engelmann, 1865) 310 pp., separately 11 plates; Beck and Krompecher (The Fine Architecture of Primary Carcinoma of the Skin, Voss, 1903), nevocarcinoma, prickle-cell, basal cell, transitional (spino-baso-cellular) tumors; Slye et al. (JCancRes 6: 57 1921) squamous carcinoma in mice and other animals, various locations Way (ADS 11 23, 1921), lattice fibers Warren (AmJPath 9 781, 1933), measurement of spindle angles in mitoses of ... malignant tissues, 91 in carcinoma, 72° ; fibrosarcoma, 84 in melanoma; Geschickter and Koehler (AmJCanc 23 834, 1935) classification epidermal, keratinizing and nonkeratinizing appendage metastasizing and nonmetastasizing, 2,100 specimens; Fidler (AmJCanc 25: 772, 1935) cancer cell as morphologic entity; Schairer (ZtschrKrebsfor 43 1, 1935) chromosome counts, variations in different tumors; MacCarty (AmJCanc 26 529 1936 J 107: 844, 1936), measurements of nucleolus-nucleus size ratio showing larger nucleolus in cancer cells; ... et al. (PSEBMC 12 257 1937) nucleolar bodies larger and more numerous in malignant cells; Page (APath ... Gruner (JLabClinM 24: 152, 1938) chromidial granules in malignant cells; Sapir (AmJPath 14 26: 309, 1938) nucleus-nucleolus ratio in tumors induced by carcinogens, ... (AmJPath 14 443 1938) morphologic variations of cells; Cowdry (APath 30: 1245, 1940) failure to establish fundamental differences between normal and malignant cells; Lucké and Schlumberger (Sci 92 418, 1940) lip carcinoma in catfish; White and Braun (CancRes 2: 597 1942) which band and crown galls in plants as neoplasms Lewis and Walton (Sci 106 419 1947) cancerous growths in invertebrates as neoplasms; Scharrer and Lochhead (CancRes 10: 403, 1950) cancerous growths in invertebrates, review Slaughter et al. (Can 6 964, 1953) "field cancerization" in explanation of multicentric origin of mucosal carcinoma.

Diagnosis.—Biopsy is the final criterion, but the clinical character of a skin lesion generally suffices for recognition. The history and the age of the patient are also suggestive. The growths are usually single and they are of slower development than inflammatory tumors. They tend to ulcerate early and are frequently covered by a thick crust. In mucosal carcinomas, the bases of the lesions are more or less indurated and generally are surrounded by leukoplakia. Lymph node involvement occurs late and is usually regional and localized.

The dangers of biopsy are hypothetical.

Small lesions should be removed in toto not nibbled at with equivocating diagnostic efforts. Biopsies are seldom necessary for diagnostic doubt can exist only when the observer is amateur or the lesion is small in which case it should be excised and examined microscopically as a whole

Needle puncture biopsy interesting although not of conspicuous clinical value in skin cancer was described by Hitch et al (SouthMJ 44: 407 1951)

It is an error to await therapeutic response in differentiating syphilis and carcinoma of the tongue.

Spinocellular cancer after ulceration shows red fluorescence in Wood's light basal cell lesions do not (Gougerot and Patte BsocfrancD 46 ... 1939) The orange red fluorescence of necrotic squamous carcinoma tissue is unique and unexplained (Ronchese et al ADS 69: 31 1954)

Prognosis depends on duration extent, location of the lesion possibility of its total mechanical removal presence or absence of metastases, and radiosensitivity of its cells. The outlook is especially grave if the growth is in the mouth. The earlier treatment is instituted the greater the chance of cure. Previous treatment that has failed greatly lessens the patient's chance of ultimate recovery

If it is possible to destroy the entire neoplasm (or with x ray to incapacitate every one of its cells) if this can be done without killing the patient, and if it is done without contaminating the operative field with viable cells even carcinoma with metastases can be permanently cured. Small growths still localized lend themselves to cure if the patient is cooperative, almost invariably In performing therapeutic destruction, which is the basis of all means of curing cancer whether surgical or radiologic, one must sacrifice normal tissue beyond the margins of tumor growth without timidity regarding cosmetic results. See also paragraphs on estimation of malignancy and classification.

Treatment.—Curative treatment of squamous carcinoma of the skin consists in the eradication of all of the cancer cells by various means. These include excision, cauterization with chemicals the actual cautery endothermy and x rays or radium. The sine qua non of intelligent therapeutic effort is knowledge of the exact extent to which one wishes to destroy and of the extent to which the agent acts, and it presupposes knowledge of the natural history of the tumor Gross and microscopic studies of whole tumor sections and clinical experience are means for obtaining such knowledge. The ideal choice [of a particular form of treatment] can be made only if all forms of treatment are available and if the choice is independent of any vested interest in an x ray machine a quantity of radium or the possession of the requisite skill and courage to undertake major surgical operations (Cade Malignant Disease and Its Treatment With Radium, Wood, 1940 see also Eller and Eller Tumors of the Skin, 1951 Lea & Febiger MacKee and Cipollaro X rays and Radium in the Treatment of Diseases of the Skin, Lea & Febiger 1946)

No competent cancer surgeon will countenance a surgical attack other than one designed to remove a cancerous growth *en bloc* the space occupied by the tumor is to be eliminated, preferably in one piece, sacrificing at the same time a margin of normal tissue intended to be adequate, if this can be done. The same principle governs x ray therapy which must deliver a tumor lethal dose to all of the neoplasm.

CAUTERY —In my practice, I depend on the Post electric cautery Properly used, I have found it to be the most valuable of all tools for combatting cancer of the skin. Many but far from all, dermatologists share this belief Under local infiltrative anesthesia, the *excision is made through normal tissues* three-dimensionally surrounding the neoplasm.

The technic of cautery excision lends itself particularly well to the *en bloc* policy for the sides and base of the wound are seared, the wound retains its shape and the field is bloodless save for vessels which require ligature. The instrument as it cuts, destroys what it touches, so that no cancer cell can be transplanted. Aseptic technic needs to be only relatively casual. The dissection can be done with nice accuracy and the intraepithelial extensions of skin or mucosal carcinoma can be destroyed with minimal sacrifice of dermal tissue and so with minimal loss of area.

The wound of a cautery excision is painless unless it becomes secondarily infected. A wound made by the actual cautery can in many cases be closed if shaped appropriately and undermined, and will heal by primary intention. Otherwise the wound may be allowed to granulate and heal, which unless it is so large as to require plastic closure it does with acceptable scarring

A disc of eyelid skin as large as a centimeter in diameter may be sacrificed without loss of area if allowed to granulate; the scar here does not contract if skin has been peeled off the underlying orbicularis muscle without damage to the muscle a procedure which with practice one can do. Thus, in the large majority of eyelid cases I use surgery where some would use radiotherapy When tarsal cartilage must be sacrificed, plastic surgery is necessary

The wound of a cautery excision, wherein decisive curative treatment is accomplished at one visit, heals within a month, and the tumor is in a bottle

of formaldehyde. Radiotherapeutic methods cannot approach this in efficiency although in some cases the scar of x ray therapy is a better scar cosmetically than that which would follow surgery

The first step in planning the minor operation is to secure local anesthesia by infiltrating the entire region of the lesion. One inserts the needle for this purpose from a point outside the outermost limits of the tumor and beneath it so that malignant cells can not be dislocated and transplanted by the administration of anesthetic. Hyaluronidase [illegible] TR units, added to 10 cc. procaine with 1 : 5000 epinephrine is sometimes desirable to aid in spreading the distribution and reducing the number of injections needed. Then with good light and a magnifying glass, one determines with deliberation where the margins of the tumor are insofar as this can be done by inspection and palpation.



Figs. 1664-1666.—Squamous carcinoma of the lip. Fig. 1664, early [illegible] leukoplakic carcinoma. Fig. 1665, small buttonlike lesion with central ulceration. Fig. 1666, more advanced carcinoma invading muscle and extending, as sharply marginated [illegible] leukoplakia, [illegible] the buccal mucosa. Such leukoplakia is part of the cancer and must be destroyed when the mass of tumor is destroyed.

Figs. 1667-1669.—One way to cure carcinoma of the lip (see Fig. 1670). Fig. 1667, the lesion as it is first seen by the physician. Fig. 1668, anesthesia by local infiltration of 2 per cent procaine with adrenalin, the needle having been inserted well [illegible] the [illegible] tissue and beneath it. Fig. 1669, excision completed with a burning instrument. The [illegible] line has passed through normal tissue beyond the [illegible] of the tumor tissue, laterally and beneath. This charred wound is painless and will heal under petrolatum dressings in [illegible] without pain, leaving a healthy scar. If the edges of the wound are undermined it may be closed with a fine continuous catgut suture.

What requires judgment, skill and experience is this initial step of deciding upon the boundary mark to be made with the scalpel. The only important error one can make is to sacrifice not enough. It is an aid, in determining the margin, to look closely at the lesion while feeling it and bending its surface so as to reflect [illegible] light [illegible] directions. This discloses edges sometimes only faintly discernible and is particularly helpful in dealing with basal cell carcinoma, where a morphealike peripheral extension may otherwise escape one's notice, although to obtain cure it must be excised.

A scalpel is used to outline the area and demarcate the block of tissue to be removed. One cuts with scalpel about halfway through the dermis, then inserts the hot point of the cautery through the dermis and, following the partial incision, cuts with the cautery along

the planned line. The cautery is pointed toward the direction of cutting so that, with tension applied to stretch the wound, the skin is lifted from beneath by the point and cutting is done quickly without charring. The entire thickness of the block of skin containing the tumor is then undercut and peeled off, the depth being always through the full thickness of the skin with a sacrifice of adipose and muscle tissue appropriate to the depth of the lesion.

A circular cautery excision as large as 2 or 3 cm. in diameter even though it bares the cartilage of nose or ear does not require closure. If it can be made, let us say from the lip or cheek, in a *relatively thin, lenticular shape, one may then, after all tumor tissue has been removed* undermine with the scalpel and close with a continuous absorbable suture. Dead space must be eliminated and a pressure bandage applied, buttering the dressing with, for example, tetracycline ointment. The patient may take tetracycline by mouth 250 mg. t.i.d. for 4 or 5 days, to forestall possible infection of the wound.

If at the time of excision one recognizes neoplastic keratosis, leukoplakia or erythroplakia surrounding the intradermal tumor, one may excise the intradermal portion with margin of from 3 to 5 mm. or so, then destroy superficially the carcinoma in situ which surrounds it, using gauze moistened with alcohol to wipe away the epithelium that has been blistered off.



Fig. 1670.—Carcinoma of the lip shown in Fig. 1667. This photomicrograph covers half of the whole tumor section, not biopsy, of the lesion, after excision with the cautery. Evidence is manifest that the line of excision has actually passed laterally and beneath the carcinoma, through normal tissues beyond the periphery of the tumor's extent. If metastasis has not already occurred, this patient is going to get well and stay well, provided intraepidermal extension of the cancer in the form of leucoplakia adjacent to the ulcer has been recognized and destroyed.

After removing the tumor en bloc and before disposing of the wound, one should examine the tissue in the gross, sectioning it in several directions with the scalpel and studying it with slight magnification, in the effort to determine whether the excision has been adequate in three dimensions. When one believes that not enough tissue has been removed in any part of the wound, it is particularly easy with cautery wounds to pick up and dissect away more tissue until one is satisfied. Retaining orientation of the removed tissue one makes 1 or more histologic sections, which show whether the excision seems or seems not to be adequate.

No instrument that makes sparks competes in accuracy with the cautery used as described. With it, one may with satisfying exactness sacrifice what one wishes destroyed and leave unharmed what one does not wish to destroy.

There is no royal road to competence in the treatment of cancer of the skin. One learns by combining competent instruction and supervision with keen interest, careful comparison of clinical lesions and gross pathologic specimens with whole tumor sections made from them, and prolonged experience with patients, records and follow up studies.

SCALPEL.—Surgical excision with the ordinary blade has become increasingly acceptable in the removal of both the primary and regional involvements (Modlin: Mo.Med 51: 364, 1954).

Since the days when I sometimes held hemostats for Elmer Twyman, who was a master of cancer surgery with the cautery and saw his lip and neck dis-

sections and the results he obtained I have retained a preference for the instrument, although its popularity among surgeons, who do major and sometimes amazing work, has considerably waned.

THE CURET in the treatment of skin cancer especially squamous, is as outmoded as escharotic pastes, although there are individuals who use both with skill and effectiveness (Osborne J 154 1 1954) In condemning these media, I am sustained by the consensus of experts and dismay only a small minority

X RAY THERAPY is widely employed. Its principal advantages consist in its selective action on malignant tissues, which in many cases resist radiologic necrobiosis less than normal structures, and the excellent cosmetic results that may follow its use In many instances the growths disappear in a few weeks or months and do not recur Tumors up to 2.0 cm. in diameter were usually cured while the average size of those which recurred was 2.8 cm reported Tice and White (JKansMS 49 324 1948) regarding their series of 308 cases, among which 4 6% sustained resultant chronic x ray ulcers that were usually readily curable by surgery

It is thought that the irradiation of sensitive tumor cells leads to their primary degeneration as in simple necrosis; refractory ones are altered in chromosome structure and this results in the development of aberrant forms of cancer (Melnick and Bachem: APath 23 67 193) Small, divided doses are cumulative in producing changes in chromosomes and genes. Coutard taught that a saturation method is most efficient, treatment being not too protracted (Martin and Martin: J 104 605, 1935) Filtered fractional doses are regarded as preferable by many authors. The dose is more likely to be too small than too large (Martin: SouthMJ 29: 221, 1936) For vegetative lesions less than 2.0 cm. in diameter, daily doses of 1,100 r at 85 kv with 0.5 mm. Al filtration for 4 or 5 doses were recommended by Martin and Wright (J 134 861 194) A dose of 300 r per day to a total of 3,600 or more is an alternative technic (Dowdy NYSJM 40 621, 1940), or 400 r twice a week (Mleschert RadiolClin 10: 166 1941) See Symposium on treatment (ADS 53: 563 ff 1946) Trying doses at 200 kv., ranging from 1,200 to 6,000 r Hale and Holmes (Radiol 48 563, 1947) cured about 94% of previously untreated skin cancers by means of doses in the 2,500 to 2,800 r range cured about 80% with doses of 1,200 to 1,800 r and gained nothing by going above 4,000 r Carcinomas of the lip, 109 cases, were treated by Ivey (SouthMJ 41: 683, 1948) using from 5,000 to 6,000 r at 200 kv with mm. Cu and 1 mm. Al filtration, giving daily doses of 300 r. All healed, no x ray burn was produced and there were 5 failures.

Single massive doses delivered to small fields were found to be small as compared with the total dose that might safely be given the same field if it were fractionated over a period of 10 days or so, by Allen and Freed (J 157: 1 71 1935) The range of safe dosage proved to be wide for small fields, and it narrowed markedly as the field size increased, so that the findings of Allen and Freed differed from those of Strandqvist. Residual radiodermatitis occurred mostly following the use of large fields, those over 50 cm. in area.

The cancerocidal dose of x ray therapy is somewhere in the vicinity of 4000 r at 120 kv sometimes less. I generally give 300 to 500 r at a dose exposing the tumor perhaps daily or twice a week or even weekly until the total dose, at 120 kv with 1 mm. Al filtration is about 3000 r and then wait to see what has been achieved An adequate margin must be allowed in shielding for the curative dose must be delivered to all the cancer cells, including those located most peripherally and most deeply Since maximum tolerable doses are necessary radiotherapeutic technic must be faultless in treating cancer Improper shielding may result in failure to cure or in terrible injuries. The calculation of the dose its administration, and the use of filters can allow of no error

A patient under treatment with x ray for carcinoma of the skin must be kept under control, seen at regular intervals of a month or so after completion of therapy and prepared psychologically for the possibility of either recurrence of the primary or metastases, which have to be dealt with promptly and surgically if they occur While this is true of radiation therapy it is also of course true of surgical therapy But the patient who is not cured by radiation is likely to be a candidate for surgery thereafter with hope for cure but with poorer prognosis than if he were a fresh case whereas a patient not cured by surgery is treated by radiation with no hope for cure even if palliation is obtained for a time

Radiation therapy is curative when it is, through necrotization analogous to that achieved by surgery With the application of x ray everything in the path of the beam is affected so that large doses leave a skeleton of anuclear tissue into which cicatrizing elements may grow With surgery someone's judgment and dexterity must be depended on as to what is destroyed and what is not the surgeon commands the situation, and this appeals to my tastes. It might happen that a tumor impossible to remove surgically should be de-



Fig. 1671 —Carcinoma of the face, before and after roentgen treatment. (Dr W L. Brosius)



Fig. 1672.—Carcinoma of the lip, showing local result of roentgentherapy (Dr W L. Brosius)



Fig 1673 —Carcinoma cured by caustic paste, used without skill or understanding of anatomy Destruction has been more than adequate.

stroyed by radical roentgenization. The procedure is as radical as surgery and this fact must be recognized by the physician and the patient The latter usually imagines he is going to get off easier with the method of attack in which he is not cut on. When surgery is used, there is no radiodermatitis to worry about later (Morrow et al. ADS 35 821, 1937)

More and more, in managing cancer of the skin, I find myself preferring surgery at the outset. Cases of basal cell carcinoma, particularly in which

I obtained 5-year cures, are turning up with recurrences in or adjacent to the x ray scar in a manner such as I am not seeing among old patients treated by cautery excision.

RADIUM is an efficient agent in attacking keratoses and superficial carcinomas. A dose of from 0 6 to 1.2 milligram hours per square centimeter without filtration, in contact with the lesion will generally cure a keratosis. An erythematous reaction of moderate severity may be expected, starting about the fifth day reaching its peak at about the twelfth, and fading The lesion peels off and the skin is smooth scarred slightly if at all, after about 40 days.

In deeply seated tumors, gamma ray methods should be employed and large exposures must be given. Cosmetic results are favorable and the agent is simple and convenient. The necessity for adequate dosage must be stressed, and much disappointment will be avoided if the dosage is generous (Cutler J 103 1204 1934) Surface application is often inadequate. In lesions of the tongue in particular surface application of radium is never adequate (Simpson AmJRoentg 34 63 1935) The use of needle implants has been well described by Cole and Driver (AmJRoentg 33 682 1935) A gamma ray dose of 6000 r is generally tumor lethal (Paterson and Parker BritJRadiol 7 592 1934) See Treatment radium

GAMMA RAY TREATMENT using radium distributed on external applicators and molds was systematized so as to deliver correct dosage in a practical manner by Paterson and Parker (BritJRadiol 7: 592-632, 1934):

The unit of *dosage* rather than of *intensity* was preferred because the total dose is the most important single facto in therapy. The *duration* of the treatment during which the dose is delivered is also important In this system, the duration of continuous radiation (or radiation for 12 hours out of each 24) is explicitly limited to 8 days or less. The r is the basis of dosage measurement. In this system, 1 000 r is the working unit, and the graphs show the requirements in various situati ns for the production of dosage in working unit f 1 000

Cutaneous Reaction depends to some extent on site, condition, and vascularity For normal skin of face or trunk the expectation is as follows

3,000 r Faint erythema
4,500 r Definite erythema
6,000 r Moist desquamation (radio-epidermitis) a reaction which lasts about 6 weeks, after which return to normal is complet
7,500 r Severe moist desquamation lasting longer than 6 weeks the borderline for ski safety
9 000 r Extremely severe reaction, likely to result in immediate or late permanent radium necrosis

Certain sites, f instance the fingers, hands, feet, shins, postoperative scar tissue such as follow breast amputation and scars of lupus vulgaris, respond igorously t these doses and tolerate lower dosages. There is some relationship between the size of the area radiated and the severity f the reaction large areas respond more vigorously to the same dose than small areas, but this fact does not appea to be practically important.

Buccal Mucosa responds to radiation in a manner which is difficult t grade. The typical response consists of temporary erythema followed by the formation of yellowish white membrane surrounded by a well-defined red margin. This reaction zone indicates the area radiated Between dosages of about 4 000 and 12,000 r the appearance does not ary greatly but the reaction period lengthens with increase in dose, and the duration of the reaction may be taken as an index of dose. Most areas in the mouth tolerate doses of as much 12 000 r applied as a surface dose only after which they eventually return to normal With doses exceeding 12,000 permanent necroses are lik ly

Epitheliomas.—In assessing the response of malignant tissue to radiation it is necessary to assess not the mere surface dose, but rather th m *imum dose received at y part of the* tumor for this is the only measure f the lethal or sublethal dose. With superficial lesions the dose level as assessed at the kin is also that at the base of the tumor With deep lesions, or in the dose level is assessed as through and through dosage when double molds are used, or is assessed as depth dosage when single pplicator i used.

A dose f 6,000 if delivered t th whole f a tumor and tumor bearing zone causes permanent resolution of th great m jority f epith liomas subject to the previso regarding the duration of exposure. This figure may therefore, be taken as a serviceable in he tumor lethal dose The absolut mi imum lethal dose is probably slightly less. Experience in most cutaneous nd normal tissue tolerance show that this dose can somehow be given in most situations t the whole f an ccessible tumor of moderat size without destroying normal tissue.

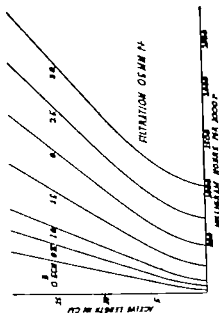
Graphs 1 and 2 (rea graph) show in milligram-hours the amounts of radi m required on flat-surface pplic tors t gi 1,000 or various areas at various treatment distances the radium being pread over an area on the pplicator *parallel* with the treated rea and of the sam siz as the treated rea, nd being *distributed i such a manner as to produce homogeneous radiation* at the stated distance.

Graphs 3 nd 4 (t be graphs) show in milligram-hours the amou ts of radium required along the central a es of ylinders of rious radii t give 1,000 t the surface of the cylinder These graphs must be read for over-all ctive length.

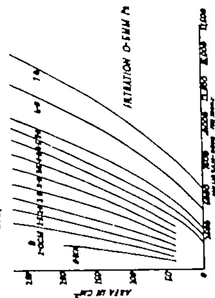
Graph reading for zero flat area or for zero cylinder length may be sed for estimations of radium needed t gi 1 0 at various distances from a point source

Distribution of radium on the pplicator is fundamentally important. *Distance* is defined as the distance separating the plane on which the radium is mounted from the plane at hich the dose i assessed *Amount of rad m* is the amount determined from the graphs, and the amount must be arranged on the pplicator The accompa ying rrangements assure homogeneity of radiation over the treated surface

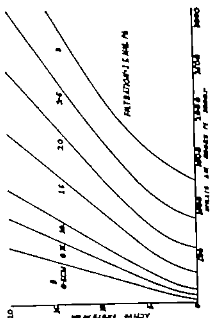
Graph 1.—Small area dosage.



Graph 2.—Cylindric applicator dosage.



Graph 3.—Large area dosage.



Graph 4.—Cylindric applicator dosage, heavy filtration.

Circles.—Use circles wherever possible. Arrange the radium uniformly around the circumference. *Employ as many radioactive foci as possible.* A circular arrangement may be considered as attaining it, with a minimum of 6 containers, a space not exceeding the distance exists between the active ends of each tube or needle.

A single circle suffices whenever the diameter is less than 3 times the distance. The circle of a diameter which is 2.83 times the distance is ideal.

Whenever the diameter is from 3 to 6 times the distance, 5% of the radium should be placed at the center.

For large areas, use 2 concentric circles and a center spot:

A. Put 5% of the total radium at the center.
B. Use percentages of radium for the outer circle as indicated in this table.

Diameter divided by distance	6	7.5	10
Per cent radium outer circle	80%	75%	70%

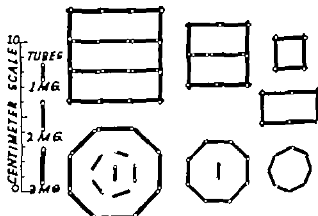
C. Distribute the remainder around a circle of *half* diameter.

For circles at small distances, the foregoing arrangement is not practical, and the following should be substituted, but is *less accurate*:

Diameter 6 to 7 times distance 10% total radium at center
Diameter 7 to 8 times distance 20% total radium at center

CIRCLES

Diameter (cm.)	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5
Area (Sq. cm.)	2	3	5	7	9.5	12.5	16	19.6	24.0	28.3	33
Circumference	4.7	6.3	7.9	9.4	11.0	12.6	14.1	15.7	17.3	18.9	20.4
Diameter (cm.)	7	7.5	8	8.5	9	9.5	10	10.5	11	11.5	12
Area (Sq. cm.)	38.5	44	50.5	57	63.5	71	78.5	86.5	95	104	113
Circumference	22.0	23.6	25.1	26.7	28.3	29.8	31.4	33.0	34.6	36.1	37.7



Typical arrangements to produce homogeneity at 1 cm. distance. (Courtesy of Dr. Paterson and Dr. Parker and the British Journal of Radiology.)

Squares.—The radium should be distributed in a line around the periphery with *uniform linear density* of milligrams per centimeter. Place active radium preferably along the whole length of any line. A linear arrangement is considered as obtaining if a space not exceeding the distance exists between the active ends of each needle or tube in line.

If the length of the side of the square does not exceed twice the distance, no further radium is required.

Additional lines should be added, if required parallel to the side to divide the area into strips of width twice the distance.

1 added line, linear density to be half that of periphery.
2 or more lines, linear density to be two-thirds that of periphery.

Rectangles.—The charts apply strictly for circles and squares. For rectangles, proceed as for squares, adding additional lines parallel to the longer side, and make a correction in the direction of increased milligram-hours, as follows:

Ratio of sides of rectangle	2:1	3:1	4:1
Percentage to be added	5%	9%	12%

Irregular Areas.—Distribute radium uniformly around the periphery. If the irregular area is roughly rectangular, add lines parallel to the longer length to divide the area into strips of width twice the distance as for rectangles. If the area is roughly elliptical, add a center spot appropriate to the mean of the two *diameters, as for circles*.

Convex Areas.—The rules apply strictly to flat areas, applicator area and treated area being equal. For curvatures up to a degree corresponding with a hemisphere or greater cylinder, all the rules may be applied, *with the proviso*: The amount of radium to be used should be ascertained from the graphs for the area treated, but should be spread over the large corresponding area projected on the applicator.

Concave Areas.—The rules as applicable to flat areas may be used, but *the area measured for dosage purposes is the area of the applicator regardless of the area treated*. Care should be taken to include the correction for the elongation of rectangles. If the applicator area is small relative to the treated area, the arrangement should be discarded and a greater distance should be employed so as to permit use of a linear source (Graphs 3 and 4) or of a point source (zero length).

Cylindric Applicators.—Radium should be mounted along the central axis and Graphs 3 and 4 employed. If possible no interval should lie between the active ends of each radium container. A space between active ends not exceeding the radius of the tube may be allowed. *For cylinders which are long in relation to their radius*, the applicator should be carried slightly beyond the treated zone. If this is not possible, an *addition of 1/10* of the total radium must be put at each end of the tube.

Single Foci.—A radium container or group of containers should be considered as a single focus, a point source if of small size relative to the distance.

Dose at Other Levels, parallel to the plane of the treated area, must be assessed in considering the depth dose delivered to the base of a tumor or in calculating dosages with "sandwich" applicators. This is obtained in units of 1,000 by dividing the number of milligram-hours actually used by the graph reading at the new distance for the area in question.

In doing this, the fact must be kept in mind that at such other distances radiation may not be so nearly homogeneous.

Filtration.—Graphs 1 and 2 (area graphs) are given for 0.5 mm. of platinum. If other filtration is used, correct as follows

Platinum (or gold)	thickness in mm.	0.8	1.0	1.5	2.0
Correction	ADD	5%	10%	20%	35%

Lead and silver figure as platinum at 60% of their thickness
Monel, brass, etc. figure as platinum at 15% of their thickness

Graphs 3 and 4 (tube graphs) are given for 0.5 mm platinum and 1.5 mm. platinum respectively. For 1.0 mm. filtration, the mean of readings from each graph should be used. For other filtration, correction factors as for Graphs 1 and 2 may be used, but they are not quite accurate.

Use of Dosage System in Practice.—In planning skin applicators, or dental molds, an attempt is made to treat an area at least 1 to 2 cm. wide of apparent tumor (as: the surgical attack demands greater accuracy) and to use a distance which will give adequate dose at sufficient depth. In practice it is found that circle distributions are easier to employ and these are used as frequently as possible. It is often practical, particularly with small lesions, to choose that distance which allows for the use of a single *ideal circle* namely the treating circle of which the diameter is 2.83 times the applicator distance. Whenever this is possible, a clinical advantage arises: the ability to expose the lesion for accurate placing, for dressings, and for manipulations through a hole in the middle of the applicator. Linear distribution are used less frequently but are useful for large areas at short distances, such as applicators for postoperative skin recurrences of breast carcinoma. It would appear on physical grounds that, for areas which are large relative to the distance, rectangular distributions may be preferable to circular ones.

In the treatment of skin lesions, such regular arrangements can usually be employed, but *within the mouth limitations of space are greater and here the rules for irregular areas find* frequent use for intrabuccal molds.

The rules for curvature allow these general principles to be applied fairly extensively but they are not applicable with safety to marked degrees of curvature, such as are found, for instance, with applicators enclosing the lip. Sharply curved applicators may be calculated *as types of the sandwich applicator*

Graphs 3 and 4 (cylinder graphs) indicate the dosage at the surface of radium-bearing tubes, as used for esophagus, body of uterus, or rectum, and for radium "corks," such as vaginal "colpostats." They are equally of value in assessing dosage resulting from any type of linear applicator

Dosage at distances from point sources of radiation, as from a sorbo ball containing radium sewed into the bladder or other cavity are ascertained from the readings for zero area or zero length of each set of graphs.

Dose in Tissue.—To obtain the dose which has been delivered at any depth below a treated surface, reverse the process of calculation and work back from the milligram-hours actually used, to find the dose delivered at the new distance from the applicator

Sandwich *Applicators.*—*It is frequently* possible to "sandwich" a growth between two molds in such a way that, to all intents and purposes, homogeneous dosage is given through and through a whole thickness of tissue, the fall of intensity of each mold being balanced by the rise of intensity of the other. When this is possible, it is desirable. To accomplish this, an applicator is planned consisting of two molds parallel to each other, enclosing between them the tumor-bearing tissue. For either mold a probable figure for milligram-hours is chosen, and the dose produced is calculated for the adjacent surface and for each successive half centimeter level of the underlying tissue. The same process is then carried out for the other mold, the doses being calculated for the same half-centimeter levels, except that, obviously they are approached from the opposite side. The doses calculated for each level are then summated and, using the figures obtained as a guide, the milligram-hours, or the distances, can be adjusted until on recalculation a uniform dosage is arrived at. The radium is usually mounted so as to produce homogeneity on the surface nearest to it, to which it contributes the bulk of the radiation. This type of calculation is the only one which is complicated. It is, however used only for extensive treatments, for which it is indispensable and which would otherwise be impractical. Once the principle is understood, it is not so complex as it appears. The "sandwich" mold principle, suitably modified, is used in making applicators for lip, cheek, alveolus and similar sites.

Cancer of the Lip.—The lesion develops from neoplastic leukoplakia (q.v.) as a rule, sometimes, however, being invasive from the start, the inception being frequently ascribed to a "fever blister" which failed to heal. Induration is typical and palpation serves well *in the large majority* of cases to delineate the extent of the primary growth. All such tissue must be excised if the attack is surgical and all of it must be resolved by radiation if x rays or radium is used. Sometimes metastasis becomes clinically manifest after the primary has apparently been controlled. This may be expected in from 5 to 10% of the cases. *A patient must be forewarned* of the possibility and his follow up must be fully controlled.

The general statements regarding treatment are applicable *to the treatment of carcinoma* of the lip. My preference is small surgical, though I use x ray therapy in higher proportion of lip cases than of cases occurring in other locations, for particularly in the small lesions the results are often very satisfactory

Invasion of the mandible in cancer of the lip, foreboded practically inevitable death in the experience of Wile and Hand (J 108: 374 1937) With the development of surgical methods which themselves have awaited improvements of anesthetic technic it has become possible to salvage some patients who not long ago would have been considered doomed. Surgery not radiation therapy is the hope of the patient who is almost hopeless.

CANCER OF THE MOUTH AND TONGUE.—The difficult problems involved require judgment which must be derived from experience and wide reading Early treatment is essential Leukoplakia and erythroplakia must be recognized—the informed dentist is a help here—and they must be adequately treated by proper destruction, chemical cauterants such as silver nitrate being generally harmful and deplorable in their effects. Richards (CanadMAJ 35 593 1936) cured over 90% of those seen early in advanced cases he was able to heal the primary site in about half the cases by the use of radiation. Worthwhile palliation may result from treating the primary by radium needle implantation even though nodes are present. In cancer of the tongue treatment originally surgical (and extremely disappointing) became radiologic with cure only of early cases, and lately has again become surgical yet the 5-year survival among patients with no nodes when treated is only about 30% and among those with unilateral nodes about 15% reported MacFee (NYSJM 53 163 1953) despite 3-stage major surgery The outlook is best in cases affecting the lateral aspect of the anterior half of the tongue The necessity for recognizing and treating tongue cancer early has been stressed by every student of the problem. Treatment of tongue cancer by interstitial radiation methods resulted in 32% 5-year arrests in 94 cases, reported Martin (SouthMJ 47 1 1954) who claimed 5-year controls in 17 8% of 56 patients with palpable nodes who received no surgery

MANAGEMENT OF LYMPHATICS.—The question may be resolved into two parts what to do when the nodes are not palpable and what to do when they are In oral cancer Padgett (Surgical Diseases of the Mouth and Jaws, Saunders, 1936) preferred to remove the nodes before evidence of metastasis appeared in them however if operation was refused, x ray treatment should be given. Wile and Hand (1937) reviewing 425 cases believed that node treatment is unnecessary unless the nodes are palpable Of 258 cases without evidence of metastasis at first visit only 8 developed it after eradication of the primary lesion, reported Hall (AmJRoentg 38 116 1937) He found that only one-fourth of the nodes which were palpable proved to be actually cancerous on histologic examination, and he denied the utility of routine block dissection. Shelmire and Fox (SouthMJ 29 489 1935) expressed my views in disagreeing with those who would resect lymph nodes in every case of lip cancer One has as much likelihood of successfully removing the early palpable cancerous nodes as of ridding a patient of cancer by removing nodes which contain tumor but which are not as yet palpable A considerable proportion of palpable nodes prove to have been enlarged by mere inflammation and recede when the primary lesion is eradicated without treating the drainage area. Hendrick and Ward (J 150 1099 1952) too, would treat nodes only when evidence of their being involved is present.

SURGERY WITH RADIATION.—It has been urged that if postoperative radiation is given, it should be done exactly as if no operation had been performed (Wintz Strahlenther 59 305 1937) Postoperative irradiation is not indicated unless the surgeon fears his work has been incomplete His fear may be justified by considerations beyond his control Preoperative radiation has fallen out of style. Moreland (J 110 1084 1938) believed that postoperative x ray is indicated if enlarged nodes which have been excised show tumor cells and in this case the radiation dose must be generous.

FOLLOW UP.—The patient must be urged to return for observation at increasing intervals for a period of 5 years. A high proportion of all the metastases which are going to occur have done so within from 2 to 2½ years.

CHEMOSURGICAL TREATMENT has been elaborated in modern fashion by Mohs (ASurg 42: 279 1941; 48: 478, 1944 53: 327 1946; Surg 21: 605, 1947; ADS 56: 143, 1947; AOphth 39: 43, 1948) He controls repeated partial destruction with a caustic by means of meticulous histologic examinations. The fixative paste contains 40 Gm. of stibnite (80 mesh sieve) 10 Gm. of powdered sanguinaria and 34.5 cc. of a saturated solution of zinc chloride "Time after time unsuspected outgrowths of small caliber from the main tumor mass were found microscopically, at times extending a considerable distance after becoming grossly invisible. (Mohs: J 138: 565, 1948.) His method has cured cases allegedly not curable by ordinary surgical or radiotherapeutic methods "because of the facility with which the ramifying radicles of the advanced cancer could be followed out. In the chemosurgical treatment of cance of the skin, microscopic control of excision is accomplished thus: (1) chemical fixation in situ of the tissues suspected of being cancerous, (2) excision of a layer of the fixed tissue, (3) location of the cancerous areas by systematic microscopic examin tion of the excised tissues, (4) further chemical treatment limited to the areas demonstrated to be cancerous and (5) repetition of the process until the cancer including all its irregular extensions, has been entirely e cised.

The method was interestingly discussed and modified by Lunsford et al. (ADS 69: 149 1953) whose presentation I attended and discussed with some skepticism.

I judge it an error of policy to chase a tumor from the midll outward.

The horrors of escharotics when used stupidly (although they can be curative) are described by Ackerman and Eberhard (JMoMA 40: 163 1943)

Podophyllin applied topically has been used as an agent of destruction, for it has a necrotizing effect on epithelial cells, affecting the process of mitosis. That it can be used in such a fashion as to cure cance was shown by Smith and Garrett (ADS 61 946, 1950) who did not argue that it should be used for the purpose. Kern and Fanger (ADS 62 526, 1950) tried podophyllin first curetting the tumor then applying the substance afte the manner of a caustic; they found it unreliable.

Colchicine, a pharmacologically related chemical, also intensively active in its in flue ce on mitosis, was tried by local injection by Nelson (ADS 63: 440 1951) who reported that it would cause the disappearance of some lesions, but was not satisfactory

PALLIATION —Sympathetic careful attention to incurable patients is appreciated. There is ample play for the art of the physician in managing the doomed. I am not successful with prevarication, and my patients regularly find out the truth and think the less of me when I try to hide it from them. A man with dependents for whom he must provide in a limited time is better served with facts than with deception What can be done for a patient who must die was discussed helpfully by Daland (J 136 391 1948)

X ray therapy for palliation is given in doses which do not sicken or cause violent reactions locally it may help a great deal.

Supportive therapy with good nutrition (the mechanics of which may be challenging in cancer of the face lip or mouth) should be maintained. Protein, vitamins perhaps isoniazid or cortisone will aid in supporting strength. Suitable antibiotics contribute materially in controlling secondary infection. Cutaneous metastases of certain carcinomas arising elsewhere may actually disappear under estrogenic hormone therapy; see Metastatic tumors in the skin (p 1305)

Opiates and other sedative and pain-relieving medication should not be withheld, although they may not be needed and should be used with good judgment (Lee J 116: 216 1941) Cobra venom by injection has been used with success in controlling pain (Körbler KlinWchn 2 1185 1934)

Alcoholic injection of the Gasserian ganglion may control pain in incurable cancer of the mouth (Harris BMJ 2: 831 1938) Cordotomy destroying sensory pathways, may be undertaken (Grant: J 116: 567 1941) The possibility of exploiting refrigeration as a means of relieving pain may be considered (Smith and Fay J 113 653 1939 AmJClinPath 10 1 1940) What the surgeon has to offer was described by Bonica (JMichSMS 52 284 1953)

Odo may be ameliorated by moist compresses of tartaric acid solution at a pH of 2.9 or diiodohydroxyquinoline tablets (Karnaky: J 122: 780, 1943) A solution of azochloramide, an organic chlorine compound, oxidizes and deodorizes a stinking ulcer and serves also as a disinfectant (Geschickter and Copeland: SouthSurg 7: 44 1938) Zinc peroxide

is likewise useful (Freeman: J 115: 181 1940) A deodorant recommended by Riordan et al. (NYSJM 42: 802 1942) consists of copper sulfate 0.15 zinc sulfate 0.45, water 10, lanolin 20 zinc oxide ointment to 100. Granulated sugar scattered over a stinking ulcer at frequent intervals was suggested by Narat (J 130: 235 1946) Chlorophyll solution was found worthless as a deodorant, by Jutscher et al. (J 157: 1279 1955)

TREATMENT.—See Erickson and Stenstrom (AmJRoentg 26 [illegible], 1931) x-ray unless cartilage is involved Merritt and Rathbone (Radiol 24 701, 1935 AmJRoentg 35: [illegible], [illegible]), 220 kv 5 mm. Cu, huge dosage Sheimire and Fox (ADS 34 [illegible], 1936) radium needle technic for skin lesions Friedman and Engel (J 106 1879 1936) vegetative lesions melted down fractionally with low voltage therapy Melnick and Bachem (APath 23: [illegible], 1937), experimental work favoring cumulative low doses, to saturation Williams (BritJRadiol 11 641 1938) 4000 r dose routine MacDonald (CanadMAJ 38 [illegible], 1938) 8 big tumors treated with x ray. Wigby and Cohen (Radiol 35 70, 1940) 83 lesions treated with radiation Moore (NoWMed 39 276, 1940) open wound low-voltage, massive-dose technic Dowdy (NYSJM 40 621 1940) lesions attached to cartilage or bone can be cured by 300 r daily to total of 3,600 to 6,000 r Hatchette (NOrlMASJ 93 [illegible] 1941), Chaoul technic; [illegible] (Radiol 37 [illegible] 1941) high-voltage therapy; Andrews and Barnes (NYSJM 42 [illegible], 1942), 300 daily for 6 doses, 166 kv with filtration, may be repeated Nelson (JOklaMA 37 42, 1944) 200 kv filtration with 2 mm. Zn, 3 mm. Al, 3 cm. wood, 6 per minute, 200 to 750 r daily to total of 3 000 to 4,000 r Smithers (X ray Treatment of Accessible Cancer Williams & Wilkins, 1946, 147 pp.) Wood (J 140 512, 1949) failures due to residual carcinoma in situ Howell (SouthMJ 43 [illegible], 1950) radium needles for skin lesions Sharp and Binkley (AmJRoentg 67 606 1952) 1 304 cases illustrating recurrence due to inadequate initial treatment, curative capabilities of surgery x rays and radium, and therapeutic technic; Lamb (J 153 1509 1953) radiation Andrews et al (J 154: 21 1954) radiation; Belisario (AustralJD 2 179 1954) skin tumors, varieties, illustrations, treatment.

CAUTERY.—See Percy (J 58 696 1912) cancer of uterus Hazen (JCutD 35 [illegible], 1917), dermatologic uses Ochsner (AnnSurg 68 [illegible] 1918), cancer of jaws, Eller (J 100: [illegible] 1933) fulguration and endotherm knife Percy (TransWestSurg Assn 44 [illegible], 1934); Jacobson (UCutRev 41 871 1937) review; Hathaway and Howard (NoWMed 38: [illegible], [illegible]), electrothermy and radiation Jacobson and Alcon (ADS 61: [illegible], 1950) review technic.

LIP.—See Clark (J 71 1365 1918) endothermy Bowen (BostonMASJ 181: 11, 1919) photographs Broders (J 74 656, 1920) comprehensive study illustrated Lain (J 75 [illegible], 1920) lip cancer comprises 2% of cancer deaths, treatment cannot be routine Lain (ADS 6 434 1922) radiation; Twyman (J 78 [illegible], 1922) surgery; Driver (OhioMJ 28 [illegible], [illegible]), individualization of treatment Duffy (AmJRoentg 29 241, 1933), statistics of metastases Molesworth (DWchn 80: 1124 1934) x-ray therapy preferred Martin (AnnSurg 10 [illegible], 1935) Kaplan and Krantz (AmJRoentg 34 [illegible], 1935) 93 cases treated with radium, [illegible] cured, Kaplan (Radiol 28 [illegible], 1937) 160 Bellevue cases; Hall (AmJRoentg 38 116, 1937), 288 U [illegible] of Pa. cases, 6.3% occurring in women of which 78% affected upper lip, radium therapy discarded in 1933 Ackerman (AmJRoentg 38 743 1937); Swinton and Trusdale (SurgClinNoAm 18 [illegible] 1938) 52 cases Wilson and Cade (BritJRadiol 11 [illegible], [illegible]) Newell (ASurg 38 1014 1939) 390 Hopkins cases; Carter (CanadMAJ 40 [illegible] [illegible]) [illegible] cures in 70 cases Blair and Byars (Surg. 8: 340, 1940) advise early treatment Lamb and Eastland (J 117 600, 1941) radium in 318 cases Martin et al. (AnnSurg 114 [illegible], 1941), 375 cases with 70% 5-year cures; Martin (AnnSurg 114 972, 1941), management of metastases Howes and La Rosa (AmJRoentg 47 39 1942) surgery or radiation may equally control primary, metastases require surgery, Schreiner and Christy (Radiol 39 [illegible], 1942) [illegible] cases, 17 in females Charteris (BMJ 1 710, 1946) 242 cases, 10 developing nodes after successful elimination of primary by radium needle implantation; Sharp et al. (J 142 [illegible], 1950) radiation therapy 250 to 500 r daily and wide excision of leukoplakia.

TONGUE.—See Taussig (ADS 6 424, 1922), 12 cases treated with radium; Solland (ArchClin CancRes 2 55, 1926) radium Cole and Driver (AmJRoentg 33: 662, 1935) radium needle implantation, technic and dosage Gardiner (BMJ 2: 1000, 1935) 33 cases, radiation as good as surgery Simpson (AmJRoentg 34 63, 1935) implantation therapy Richards (CanadMAJ 35 [illegible], 1936), 101 cases, necessity for early treatment; McDowell (MJAustral 2 [illegible], 1936), 33% cured, but radium therapy is worth-while palliation even when nodes are present Martin (AnnSurg 105 418 1937) 98 cases, 67% with nodes when first seen, [illegible] of those with positive STS dead within 2 years, 20% 5-year survivals; Sching and Zuppinger (also [illegible] p 411) 203 patients, 16 of them women, seen 1919-1935, only 6% of those treated prior to radium living longer than 1 year after diagnosis, [illegible] survived 1 year or more after radium needles were used Duffy (AmJRoentg 39: 767 1938) 252 tongue, 1,263 mouth cases, Memorial Hosp., surgery preferred if operable, but advanced cases live longer and more comfortably with x-ray therapy Wilson and Cade (BritJRadiol 11: 599 1938), threshold dose less than 0.45 per minute Sachs (AmJRoentg 42 [illegible], 1939) 79 cases with regional proved nodes [illegible] Martin et al. distant metastases in 4, to lungs, sternum, vertebrae, pleura, omentum, skull Martin et al. (ASurg 41 [illegible], 1940) 556 Memorial Hosp. patients, average age 54, 87% males, [illegible] positive STS unless tumor was small and situated at the edge of the anterior half of the tongue prognosis was bad Jorstad (JMoMA 38 [illegible], 1941) brief review, necessity for early treatment Richards (AmJRoentg 47 191 1942) 167 cases, definition of stages, indications for surgery and x ray; Sharp et al. (WestJSurg 58: 257 1950) 31 cases Bakamjian and Sayago (AmJRoentg 71 [illegible] 1954), 112 cases, 15 of them women, radiation for primary, surgery for nodes Howell (BMJ 1 420, 1954), 673 tongue cases, 916 buccal, [illegible] pharyngeal, radium or deep x-ray Manchester 1932-1942, showing significantly better response by women than men.

MOUTH.—See Plummer Vinson syndrome, Blair and Moskowitz (InternatJOrthodont 9 [illegible], 1923) Driver (OhioMJ 24 [illegible], 1933) factors influencing choice of therapy, Martin and Pflueger (ASurg 30 731 1935) 99 cheek cases, [illegible] cured Richards (CanadMAJ 35 [illegible], 1936) 168 cases, various oral locations Padgett (JMoMA 33 [illegible], 1936) [illegible] preference for males before metastasis is evident Figi (JAmDentA 23 216, 1936), [illegible] Ackerman (AmJRoentg 38 [illegible]) tobacco contributes [illegible] of cancer deaths are cancer of mouth [illegible] 43 1937) shielding important as destroying; Padgett (JOrthodont 23: 203 [illegible]) epidermoid carcinoma in 716 [illegible] 1937), monographic on [illegible] cases, curing one-eighth of and about the mouth Chance (IrishJMSc [illegible] 146, 1939), 539 cases, [illegible] Kennedy (Am those of tongue Gardham (Lancet 1 677 1939) classification and prognosis [illegible] (AmJSurg 57: [illegible], 1942) [illegible] Surg 114 [illegible] 1941) surgery offers hope Martin and Koop (AmJSurg [illegible] 1942) 75% of chronic oral Memorial cases, benefits of [illegible] Keyes (AmJSurg [illegible]) control primary and do block dissections ulcers are cancer Mayne (AmJMedSci 210 [illegible], 1945) distant metastases to lungs, bones, even heart, now seen more often since local therapy has become fairly effective Castigliano and Rominger (AmJRoentg 71: 997 1954)

BASAL CELL CARCINOMA

Symptoms.—The comparatively benign variety of carcinoma of the skin develops from basophile cells resembling those of the basal layer of the epidermis and the accessory structures of the skin (see pilosebaceous adenomas). It does not metastasize except in extremely rare instances. The rate of de-



Fig. 1074.—Basal cell carcinomas. *A*, A small eroded nodule. *B* An inactive, deeply seated, dangerous and difficult lesion. *C* Multiple superficial basal cell epitheliomas. *D* A small but classic lesion of the occipital region. *E* A large vegetative tumor. *F* An eroded nodule with pearly border on a young woman's chin. *G* An extensive, sclerosing, morphea-like lesion with typical peripheral dyke and shiny atrophy within.

struction is not so great in this as in the squamous variety but ulceration is progressive. Men are attacked more commonly than women. Most cases occur in adults by predilection on the face, especially on the nose and eyelids, but they may develop anywhere on the skin, almost never on mucous membranes. The etiologic factor influencing location is not well defined as is

the *influence of sunlight* in the etiology of squamous lesions. Nose forehead, upper lip eyelids and covered parts of the trunk and extremities are preferred.

Basal cell carcinomas usually appear first as small shiny whitish or reddish, *translucent nodules* indistinguishable from those of epithelioma adenoides cysticum (p 1152) They less commonly begin as scaly patches. Lesions may be *single* or *multiple*. They give rise to no symptoms until after persisting







Fig 1675.—Basal cell carcinoma of the ear. Stretching the skin enables one better to determine the actual extent of tumor in vasion. The extent is not indicated by the extent of ulceration (Dr J P Guequierre)

Fig 1676—Basal cell carcinoma of nose, with beginning ulceration

Fig 1677—In an e basal cell carcinoma of nose.







Fig 1678.—Basal cell carcinoma at angl of nose

Fig. 16 9—Basal cell carcinoma at inner canthus, on nose y t excise th the cautery

Fig 1680—A large, eget tl basal cell carcinoma.

for weeks or months, they undergo ulceration When this occurs, it first involves the central part of the growth and the remainder slowly spreads peripherally Ulcerated areas may heal slowly leaving smooth or scaly atrophic cicatrices but progress continues at the periphery While spontaneous partial healing is commonplace complete recession of a basal cell tumor is extremely exceptional A pearly waxlike border and central crusting are classic features, the rolled margin being discernible though this, even in superficial basal cell lesions as a rule The clinical appearance may be




Fig. 1681.—Basal cell carcinoma of upper lip. (Dr. Stuart Way.)
Fig. 1682.—Basal cell carcinoma of a woman's upper lip, with involvement of the mucosa by extension.




Fig. 1683.—Basal cell carcinoma of woman's upper lip: an intradermal, waxy discoid nodule not ulcerated.
Fig. 1684.—Morphea-like basal cell carcinoma of a woman's face. During 20 years, progress from a central point led to this state in which one sees scar that developed spontaneously and two nodules of ulcerating basal cell carcinoma. Nodule on lower lip was seborrheic keratoma.






Figs. 1685-1688.—Basal cell carcinomas. Only the one on the left is easy to cure. Note in Fig. 1687 the extension of tumor about the palpebral margin, through loose tissue mechanically easy to invade.

widely various in unusual tumors. Diffusion of basal cell carcinoma occurred in grafts placed in the eyelids to correct contractures from a burn (Speth MaineMAJ 43 6 1951)

It has been suggested that basal cell carcinomas are located by preference at places especially liable to dysontogenetic development as dermoid





Fig 1690.—Large vegetative, nodular lesion, easy to cure surgically (Dr J P Ouquierra.)

Fig. 1689 —Nasal tumor but no ulceration as yet.





Fig. 1691 —Multiple basal cell carcinomas.

Fig 1692.—External recurrent, sclerosing and nodular lesion of nose

cysts are (McFarland et al. AmJCanc 25 273 1935) I do not subscribe to this view They may occur anywhere A statistical study of location in 500 lesions was given by Sutton (JMoSMA 39 203, 1942) see Carcinoma, location (p 1203)

Location may be quite unusual. The anal region was the site of 2 reported by Lawrence (ASurg 43: 88, 1941) who found 4 others in the literature; 4 in this location were among 237 cases of Wakely and Childs (BMJ 1: 787 1949) of whose cases 210 involved the face. A lesion of the palm was reported by Book (BJD 62: 467 1950) and of the sole





Fig. 1693.—Basal cell carcinoma, untreated, sclerosing, with nodular periphery of right mastoid region, easy to cure surgically

Fig. 1694.—Morphea-like basal cell carcinoma, extensive, curabl only by surgery





Fig. 1695.—Palliative effect of radium treatment of advanced squamous carcinoma in an old man. The lesion as first seen.

Fig. 1696.—The lesion shown in Fig. 1695, tw months after 50 mg. of radium in gold capsule had been set for 8 hours at the center of the defect, supported there by cork. The carcinoma later caused the patient' death. A 12-hour dose might have been better Plastic surgery would be expected to be curative.

by Pascher (ADS 67: 108 1953) and Pascher and Sims (ADS 69: 475 1954) suggesting that etiology lies not invariably in abnormality of the pilosebaceous apparatus. Among 4 400 skin tumors, I have seen only 4 basal cell lesions of the dorsum of the hand. The male nipple was the site in a case of Sobel (ADS 60: 81 1949) who noted that only 1 like it was among the 264 tumors of the male breast collated by Wainright (Surg 14 844 1927). The trachea was the site in 2 obstructive cases reported by Cass (Gu Hosp Rpts 88: 39_ 1938). The similarities of basal cell carcinoma and some adamantinomas and Rathke's pouch tumors (craniopharyngeomas) deserve mention.





Fig. 169.—Huge basal cell carcinoma destroying posterior half of scalp. (Dr J. W. Perkins.)

Fig. 1698.—Extensive rodent ulcer destroying bridge of nose and orbit. (Dr L. Habersteader.)

Fig. 1699.—Rodent ulcer which has destroyed antrum and palat. Adequate surgery still might cure. (Dr H. N. Cole.)





Fig. 1700.—Basal cell carcinoma, untreated, in recluse finally induced to undergo treatment in 1932

Fig. 1701.—Rodent ulcer illustrati of destruction of which it is capable prior to killing the patient. (Dr Anstruther Davidson.)

Fig. 1702.—Massiv egetati basal cell carcinoma of face. (Dr William H. Jay.)

Accessory Structure Basal Cell Carcinomas are thought to arise from hairs sweat glands, or sebaceous glands in some instances. Malformed or anomalous accessory structures seem to act as initial lesions which, in assuming active growth after prolonged quiescence become carcinomas.

Some authorities think that all basal cell carcinomas arise from pilosebaceous structures (see pathology). Mallory (J ... 1513 1910) and Hay

thorne (AmJCanc 15 1969 1931) emphasized the analogy to pilar units in the differentiation of the tumor tissues, and Wallace and Halpert (CancRes 10: 246 1950) called them trichomas to indicate the hair anlage origin they hypothesized. Wallace and Thomas (TexasSJM 47: 213 1951) insisting that they all arise from skin appendages and never metastasize (of which views neither appears to be correct) believed that they should not be considered cancerous, despite their ability to kill by unremitting extension.

Morphea-like Basal Cell Carcinoma.—Intracutaneous, steadily progressive lateral extension is typical of this variety The advancing margin is bandlike and the scarred area is smooth flattened and ivory-colored, superficially resembling scleroderma. There is usually a characteristic, raised, pearly wax like border Histologically these are of trichoepitheliomatous structure Cicatrization may be sufficiently potent to encompass tumor cells within dense



Figs. 1762A and 1762B—Inflammatory basal cell carcinoma, a recurrence at periphery of upper-lip graft.



Fig. 1762C—Inflammatory basal cell carcinoma, section from patient show in Figs 1763 and 1764. Some tumor cells ppear to lie within channels lined with endothelium.

fibrotic walls, so that some of them atrophy and perhaps disappear Self healing depends on this process, but it is indeed rarely productive of com plete cure

Most of the 33 cases studied histologically by Caro and Howell (ADS 63 53 1951) occurred on the face or neck. They found 2 cases of squamous carcinoma behaving in this fashion. Long attenuated strands of cancer cells lay in the dense fibrotic stroma and senile elastosis of various degrees was common to all the sections examined Connections between the epidermis and the tumor were sometimes impossible to find, reported Lapière and Piérard (AnndeD 81 365 1954)

In the treatment of this type of tumor excision grafting if necessary is the correct procedure The edge of the tumor is hard to determine but it must be circumvented, and within the border however wide this may be, the

skin must be removed full thickness. This will cure for seldom in the morphea like tumors does cancer invade the adipose layer Radiation therapy is unsatisfactory the dose which cures the cancer destroys the dermis, which it is better to sacrifice surgically to begin with.



Fig. 1704.—Fibroepithelial tumors, numbered 9 and 10, along with several verrucae senilis (Pinkus ADS 471 598, 1953.)

Fig. 1 05 —Struct re of lesion 10 of Fig. 1704 The t mor consists of newly formed fibrous tissue lacking elastic fibers and compressing the epithelium into thin stra ... beds of epitheli m lik that of basal cell carcinoma in B nd C (Dr Hermann Pinkus)

Fibroepithelial Tumors.—Lesion obtained from the tru k were described under this title b Pinku (ADS 6 ; 509 1953) as be g represe t tiv pe haps of several variety of basal cell carc noma. They showed permeatio of the dermi with strands of epithelial tissue resembling that of the basal cell tumor with whi h I tentatively class fy them. The derm l papillae w re enlarged so that the fibrou stroma wa excessive a d the reticulated d sem nation of epithelium through it conduced to a resemblance to intra

canalicular fibroadenoma of the breast. The lesions seemed not to possess malignancy. Two cases were reported by Degos and Hewitt (AnndeD 82: 124 1955) who classified them, as I do, with the unusual varieties of basocellular epitheliomas.

Inflammatory Basal Cell Carcinoma exists, analogous to inflammatory carcinoma of the breast wherein carcinoma extends in narrow strands in tissue spaces and vessels, as in the case of Anderson (ADS 54: 223, 1946) In a woman I saw the tumo recurrent in the upper lip, produced sharply marginated, macular redness which spread slowly onto the cheeks the tex ture of th involved tissue was only slightly more dense than normal. Curiously cortison palliated her symptoms.

Pigmented Basal Cell Carcinoma.— Melanotic rodent ulcer was the title given by Johnson (JCutD 23 65 1905) This is a type of basal cell tumor associated with pigment easily confused with melanoma unless his *tologic study is made.* Almost all basal cell tumors contain some pigment, but sufficient is present in only some 6 to 10% of them to justify the particular designation of pigmented (Gaté et al AnndeD 8 337 1937) Differing

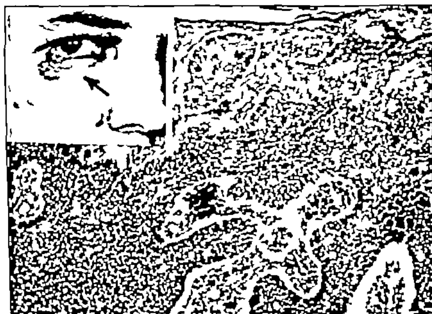


Fig. 1 94.—Pigmented basal cell carcinoma the lesion of the lower eyelid nd the microscopic structure of it Pigment is seen blackening many cells of the stroma. (Eller and Anderson ADS 27: 277 1933.)

from the pigmented acanthotic nevus (q v) these comparatively benign lesions have the prognostic features of basal cell carcinoma, not of melanoma. The pigmented cells, scattered among *the epithelial ones and also in quantities* in the stroma, are distinct from carcinoma cells, are dendritic in form and are filled with melanin granules (Eller and Anderson ADS 27: 277 1933) Pig mentation may be solid or spotty and clinical distinction from melanoma may be impossible. Most of these lesions are located on the face or neck, as evi denced by the 66 cases occurring in a series of 1,780 skin tumors studied by Birrell (AustralNZJSurg 22 47 1952) *who observed that pigmentation re*mains after cure by x ray

Caudière (Annd anatpath 3: 119; 134 1926) observed hyperplasia of the normal Langerhans' cells f the epidermis in some basal cell tumors. Bloch (AfDuS 153: 20, 1927) reported 4 cases of benign, non-nevoid mela oepithelioma of the skin. The patient of Castello (ADS 19: 691, 1929) was typical, as was that of Netherton (ADS 37: 319 1938) in whom pigmentation remained aft pparent cure with radium therapy Cipollaro et al. (NYSJM 43: 1931 1943) presented a case and reviewed the literature Duany (bs BJD 42: 241 1930) collated 4 cases, noting that the lesions are ften multiple and are well known to ophthalmologists because of their occurring at the limbus.

Multiple lesions were present in the case of Nomland (ADS 25 1002, 1932) having arisen from numerous pigmented lesions present since birth presumably epithelial nevi. Another woman with similar lesions was seen by Nisbet (ADS 47: 372, 1943) the tumors presenting the filigree architecture of some seborrheic keratoses. Many tumors some of them pigmented were scattered over the body and scalp of a young man reported by Woringer and Renard (AnndeD 8: 38 1949) See Multiple basal cell carcinomas.



Fig. 1707.—Multiple, superficial basal cell epitheliomas. (Dr J Lamar Callaway)





Fig 1708.—Superficial basal cell epitheliomas in a psoriatic, previously long treated with Fowler's solution.

Fig 1709 —Superficial carcinomatosis in a farmer from arsenic absorbed from sprays. The ulcerating carcinoma over the scapula eventually was fatal.

Pigmented basal cell carcinomas sometimes afford clinical not histologic diagnostic problems, but are not different with respect to prognosis and treatment from other basal cell carcinomas. Multiple superficial lesions are sometimes pigmented, like the case of Brodey (AD 71 130 1955) as multiple tumors arising from epithelioma adenoides cysticum (p. 11?) may be too.

Multiple Basal Cell Carcinomas may arise in cases of epithelioma adenoides cysticum (q v) resulting in an astonishing clinical appearance Such have been described by Paul (Cutaneous Neoplasms, Lewis, 1933 p 46) Scott (BJD 64 342, 1952) Calnan (BJD 65 219 1953) and others. Zosteriform arrangement of multiple lesions has been noted by Adamson (BJD 29 81 1917 64 345 1952) and by Witten and Lazar (BJD 64 97 1952) Multiple lesions are usual in superficial basal cell epitheliomatosis (q v)

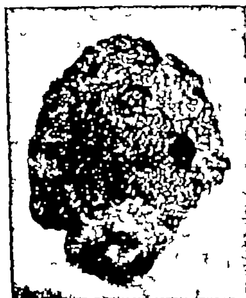




Fig. 1710.—Superficial basal cell carcinoma, showing mass of subepithelial tumor strands, a few of which have undergone shallow ulceration. (Dr J Lamar Callowav)

Fig 1711.—Superficial basal cell epitheliomatosis Little aggregates of tumor tissue of basal cell type are seen in the superficial portion of the dermis.





Figs. 1712 and 1713 —Superficial basal cell carcinoma.

Superficial Basal Cell Epitheliomatosis is characterized by the development of superficial sharply circumscribed patches of scaling dermatosis simulating patches of psoriasis, generally on the trunk. The color is reddish, the outline irregularly oval, the scaling irregular the margin definitively sharp if carefully examined, the duration considerable, and the symptoms slight or absent consisting of more or less itching and chronic annoyance The patches enlarge by irregularly centrifugal spread, unresponsive to the various salves

with which they are plied. Eventually large enough masses of tumor tissue aggregate to form nodules which undergo central necrosis, and ulcerative basal cell cancer then progresses. One several, or many superficial basal cell carcinomas may appear on one individual Their fine threadlike rolled, pearly border is typical.

The description by Fordyce (J 55 1624, 1910) anticipated all others I know Many multiple epitheliomata in the early stages resemble Paget's disease They present all grades from pale and red scaling patches the size of a split pea or smaller to patches as large as the hand. They have sharply defined scalloped margins, showing very slight tendency to elevate or pearly rolled edge Some of them maintain their red and scaling appearance and others become the sites of fungating growths.

Etiologically the relationship of arsenic to their causation has been stressed by Anderson (ADS 26 1052 1932) Montgomery (ADS 32 218 1935) and others. With them, I am convinced that arsenic is likely to be implicated see Carcinoma, etiology The presence or absence of demonstrable arsenic in the lesions themselves does not prove or disprove the relationship it is recognized that carcinogenic agents initiate cancerous change, then play no further active role.

Microscopic examination shows tumor tissue of basal cell type closely applied to the undersurface of the epidermis in apparently *isolated clumps*. *Appreciation of the* lesion as a solitary thing is facilitated by looking at it repeatedly from a distance of three feet over a considerable lapse of time rather than cutting it vertically and examining it ones from a distance of a millimeter Sections perpendicular to the skin have been interpreted as showing multicentric origin, but sections parallel with the surface indicate that the tumor tissue forms a network spreading radially at the dermo-epidermal junction and apparently unifocal in origin (Madsen: Acta D-V 21 514, 1940; 22 4 1941; AD — 29 1955)

This carcinoma has a central place of origin, from which it grows continually in radial (peripherad) direction along the interpapillary processes or ridges in the epithelium. The tumor degenerates in pieces centrally, thus leaving isolated isles of carcinoma (of which a few only are connected with hair follicles) while the tumor tissue in the peripheral region of the patch forms, practically speaking a continuous belt. Similar facts are true of Bowen's type of superficial squamous epithelioma. "Situation next does not imply derivation from (Sutton: ADS 46: 1 194_) Beneath the tumor epithelium, his is definitively unlike the normal despite its juxtaposition to it, there is inflammatory infiltration of the dermis as in any epitheliomatous lesion.

Treatment is best undertaken with local or general anesthesia and superficial destruction with the actual cautery accomplishing a complete removal of epidermis from the lesion and a small margin of adjacent normal skin. It is seldom necessary to excise these lesions. *Radiation therapy* is suitable only for the small ones and is erroneous in the treatment of extensive plaques. If it is used the dose should be a single, caustic one such as 1,000 r

Intraepidermal Basal Cell Carcinoma is recognized (Borst Verhandl deutschpathGesellsch 7 118 1904 Jadassohn BeitrklinChir 136 345 1926 Montgomery ADS 20 347 1929 Sims and Parker ADS 58 4 1949 Haber and Seville BJD 65 321 1953)

The lesions simulate senile keratoses or psoriasiform superficial epithelioma. They may be solitary or multiple They are scaly for the growth of tumor tissue is expended on the production of material which flakes off with moderate generally greasy cohesiveness rather than the hard harsh scaling of the senile keratosis. They are sharply marginated histologically as well as clinically

Microscopically one sees masses and whorls of cells identical with those of ordinary basal cell tumors, commingled with and pushing aside the cells of the normal epidermis, which on that account bulges and is distorted.

The lesions may eventually invade becoming ordinary basal cell tumors intraepidermal spread sometimes occurs at the border of an otherwise ordinary lesion. When intradermal invasion takes place the tumor is likely to show considerable sclerosis of its stroma.

Cure is accomplished by destroying the growth completely and this can be done, when extension has not exceeded the intraepidermal phase, by applying the cautery superficially as in the treatment of seborrheic keratoses, with which the lesions are readily confused clinically A peeling dose of x ray therapy 1,200 r more or less, will accomplish the same result.

Basal-Squamous Cell (Intermediary Cell) Carcinoma.—Tumors are frequently seen in which are combined the characters of basal cell and squamous types of structure They cannot be identified clinically but histologic study reveals the transitional character of architecture as of a basal cell tumor with intermingling basal and keratinizing cells.

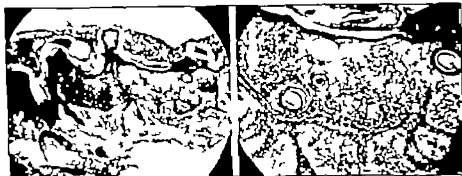


Fig. 1714.—Intraepidermal carcinoma. Clinically this was a slightly elevated, seborrheal, brownish plaque on the neck, a chronic anomaly which had changed little in many months.



Figs. 1715-1717.—Basal-squamous carcinoma. (Dr Hamilton Montgomery)

This type of growth was recognized by Krompecher (The Fine Architecture of Primary Carcinom of the Skin Vogel, 1903) and elaborated upon by Darier and Ferrand (AnndeD 3: 385, 1922) who described as épithélioma métatypique the lesions in which prickle cells, not found in true basal cell lesions, occur MacCormac (BMJ 1: 457 1924; BJD 5_ 141 1940) was concerned with these lesions, which seemed sufficiently commonplace t justify th inquiry as t whether there are several types of carcinoma of the skin o nly 1 basic kind with intergradient transitions of variety Among 1,0?? skin cancers, these comprised about 7% of the series of Welton et al. (ADS 60 ?77 1949) Montgomery (ADS 1? 50 1928) in an extensively documented review howed that th lesion re capable f metastasis in some nstances and require treatment appropriate for squamous carcinoma. He wrote: "Basal cell epithelioma is not a morphologically closed entity but may through metamorphosis become a basal-squamous cell epithelioma o even a squamous cell epithelioma. Transitional epitheliomas, presenting features of both basal cell and squamous epithelioma, occurred in 1.6% of a series of 119 cases They rep ese t metamorphosis of basal cell epithelioma into squamous cell pithelioma and are not de-

generative forms of the latter In a series of basal cell epitheliomas diagnosed clinically as such, some 15 to 20% will probably prove on microscopic examination to be transitional. Basal-squamous cell epithelioma is not, as a rule, the result of roentgenotherapy although the latter may be a factor in increasing the degree of malignancy of a tumor. In 60% of the cases these transitional epitheliomas are clinically indistinguishable from basal cell epitheliomas, the distribution and course of which they approximate. Most if not all cases of so-called metastatic basal cell epithelioma will prove on microscopic examination to be basal-squamous cell or squamous cell epithelioma. Basal-squamous cell epithelioma is relatively resistant to roentgen ray and radium treatments as compared with basal cell epithelioma. Surgical treatment with an unusually wide excision because of the insidious infiltration of the tumor cells is indicated whenever possible They are prone to recur"

Angiomatous (Hemorrhagic) Basal Cell Carcinomas constitute a rare form characterized histologically by cavernous angiomatous spaces surrounding the basal cell proliferations. These grow and expand into the subcutaneous tissue are usually adherent to the epidermis, which may be elevated and discolored with a bluish hue, are encapsulated, and may feel cystic (Geschickter and Keasbey AmJCanc 23: 568, 1935 Lamb et al: South MJ 36: 132, 1943) Not radiosensitive they are readily cured by excision.

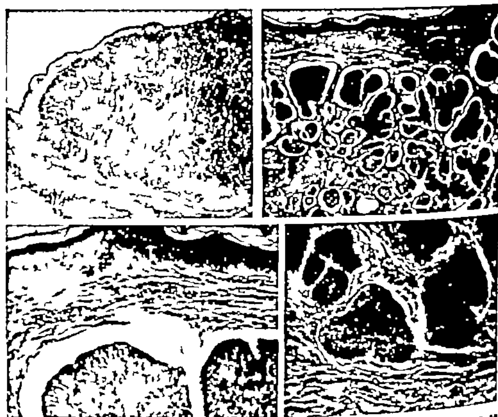


Fig 1 18—Lipoma like basal cell carcinoma, a soft tumor 2 cm. in diameter on an old man neck Note that the tumor is entirely beneath the papillary layer of the dermis which is stretched flat The stroma is not inflammatory (Sutton ADS 45 176, 1942)

Lipoma-like Basal Cell Carcinoma is a rare sort in which the adenoid stroma, similar perhaps to that of cylindroma (q.v.) forms a soft, bulging subcutaneous mass elastic and lipomatoid on palpation, identified by histologic not clinical, examination (Sutton: ADS 45 176 1942)

Metastatic Basal Cell Carcinomas have been observed in which regional lymph node involvement apparently has not resulted from mere extension. Such are extremely rare (see MacCormac (BMJ 437 1924) DeNavasquez (JPathBact 53: 437 1941); Genkel (also BJD 66 193 1934) Most of the few cases have (ADS 56 172, 194) originated in the scalp. One of the 2 reported by Lattes and Kessler (Canc 4: 866, 1951) followed a burn of the scalp in a young woman, and regional node involvement spread to the brachial plexus and finally to the lungs, resulting in death 1 years after onset. Their other case involved the wrist of a young man, produced axillary metastases 14 years later and despite amputation caused death with distant metastases 22 years after onset. They found 18 other cases in the literature. Compare craniopharyngeoma.

Etiology—Basal cell carcinomas usually represent, it seems, progressive growth of such anomalies as epithelioma adenoides cysticum. A history can generally be obtained of a preceding lesion a waxy pimple or blackhead like lesion which the patient has picked. A lesion clinically a keratosis, probably in reality a superficial or intraepithelial basal cell carcinoma, may be the initial lesion, a scaly patch rather than a waxy papule Sun exposure, x radiation and absorption of arsenic predispose as they do to squamous lesions. Histologic structure cannot accurately be predicted before the microscope is used. The relationship between the tumors in multiple basocellular carcinoma is an interesting one they appear to represent progressive growth of individual anomalies.

Trauma appears to be concerned with the inception of basal cell carcinoma more commonly than of other cancers. Among 41 cases, 5 suggesting this relationship were reported by Schrek (APath 31: 434 1941) and 1 was noted by Reah (BMJ 2 412, 1947) Patients commonly give a suggestive history see also Carcinoma etiology trauma (p 1213) and the last paragraph of Treatment hereinafter



Fig. 1719—A small, nonulcerative, waxy nodule showing [illegible] of pilosebaceous dysontogenesis. Tissue which parodies hair is seen at the left, tissue which parodies sebaceous gland at the right.

Pathology.—The development of the cancer masses can be studied best in small lesions. The process apparently begins in the basal layer of the epidermal or follicular epithelium. Tumor tissue can be distinguished readily from normal to which it may lie adjacent. The configurations of cell congeries seem governed to a considerable degree by the mechanical features of the surrounding structures, the course and progress of the cancerous masses being dependent on the density of the tissues. Long sinuous strands of cancer cells may extend far into the dermis. They may coalesce.

The fibrotic reaction of the dermis may be of various degrees, in some 10% of the lesions being considerable (Umiker and Director ADS 69 486 1954) so that there may be more stroma than epithelioma and the lesion is clinically of the morphea like type (q v) These are the tumors which are infiltrative and tend most to recur after surgery (Thackray: BritJCanc 5 213, 1951) Epithelial lumps are often acorn-shaped, ocasionally with a cystic, mucoid center which consists of disintegrated cancer cells. There is a tendency for the peripheral epithelial cells to form a palisade arrangement. The resemblance to hair matrix sebaceous gland structure is often suggestive.

Krompecher (Beitrpathanat 28 1 1900) described lesions characterized by solid pouchlike downgrowths, by cysts, by adenoid filigreed strands, and by nests forming parakeratotic pearls.

Fig. 1720.—Basal cell carcinoma, structure. *A* Vegetative, crusted lesion consisting of masses simulating sebaceous glands and undergoing mucinoid cystic degeneration. *B* The rolled, pearly border and central ulceration have their histologic counterpart; the periphery of the tumor is definitive, so that it is possible to excise thereby adequately and so cure. *C* Trichoepitheliomatous structure, the entire surface being composed of lacy strands of carcinoma tissue. *D* Whole tumor section of 4 mm. waxy papule from tip of nose.



Fig. 1721.—Tiny basal cell carcinoma from nose whole tumor section.

The stromal type, myxomatous, intermediate o densely fibrous is an additional histologic characterization (Telow: ADB 68: 403, 1953) Mitoses may be few o many The slower-growing tumors of Telow's series generally occurred in the younge patients and showed peripheral palisading and cystic or denoid architecture. In slow growing lesions, round-cell infiltration in the vicinity is less than in fast-growing lesions. A thin layer of connective tissue frequently separates the tumor mass from the subpapillary stroma.

Commingled with the tumor cells and in the stroma one may find dendritic, pigment containing cells; if they are numerous the lesion is called a pigmented basal cell carcinoma (q.v.) Squamous differentiation of various degrees may be present, so that basosquamous carcinomas (q.v.) are relatively common. The cells themselves re relatively basophilic, often spindle-shaped, and loosely or compactly grouped, and lack spinou processes and intercellular bridges.

Degeneration of basal cell carcinoma epithelium in the larger aggregates is often productive of a mucinous stuff and superficially located masses may on this account constitute actual vesicles. Vesicular basal cell carcinomas are particularly common about the eyelids. Degeneration is sometimes productive of eosinophilic material similar to the content of a sebaceous cyst this may exist in large masses, in which cholesterin clefts may be found, or in small quantities representative of solitary deceased cells. Calcification of this material may occur



Fig 1112.—Sclerosing type of basal cell carcinoma, half of a whole tumor section. Note histologic evidence of necessity for wide excision and for removing entire thickness of skin.

Efforts to demonstrate the point of origin of the neoplastic epithelium from its source have generally succeeded in showing microscopically that normal and neoplastic epithelial cells lie adjacent to each other Some observers read into the histologic preparations a transition from normal by gradual stages into the abnormal; others see that the two kinds are distinct though commingled, to some extent, where they are in juxtaposition. No one has ever seen tumor epithelium being derived from normal.

Accessory structure similarities are such that Foot (AmJPath 23: 1, 1947), confirming Mallory (J 55: 1513, 1910) Haythorn (AmJCanc 15: 1969, 1931) and Loos (AfDeS 174: 465, 1936) recognized the analogy of basal cell tumor development to pilar sebaceous and sudoral units, with variation in differentiation. He classified "adnexal carcinomas among these types: (1) pila proper primordial, or cylindric; ( ) sudoriparous, adenoid or hydradenomatous; and (3) basal-cell. Any may be pigmented. A rich, nonmyelinated neural plexus is present in the tumors, which begi by loosening of elements of the rete near a hair or sweat gland, followed by the formation of small nodules in the dermis just outside the basal layer Pinkus (JInvDerMS 37: 533, 1938) classified the lesions according to whether their structure resembled epidermis, hair follicle, sebaceous gland or sweat gland, a d whether the differentiations were considerable, intermediate or meager

Classification of tumors originating from the primary epithelial germ was undertaken also by Lever (ADS 57: 679 709, 1948) who explained the wide ariety of histologic pictures by variations in degree and direction of diff rentiation prior to the onset of neoplasia. Lever discussed organic, organoid, suborganoid and nonorganic hamartomatous tumor formation, each class being subject to sebaceous, apocrine or pilar differentiation.

His organic hamartomas are organoid nevi; his organoid hamartomas are adenomas; his suborganoid hamartomas are benign epitheliomas; and his nonorganic hamartomas are basal cell epitheliomas, which he would not call carcinomas because they do not metastasize. The tumor cells were clear cuboid and arranged in a papillary manner in 4 of 700 lesions studied by Liu (AmJPath 25 93 1949) A curious honeycomb layer surrounded the tumor masses, which resembled sebaceous adenoid tissue in the unusual lesion reported by Hoffmann (DWchn 1-5: 459 1953)

Diagnosis.—The sharply defined and waxy character of the lesions, the absence of lymph node involvement, the comparatively slow growth rate and the tendency to progress laterally help to distinguish them from the squamous variety When the skin is stretched and suitably illuminated, the tumor tissue gives an appearance such as would an intracutaneous injection of paraffin. Histologic diagnosis is essential. The absence of apple-butter nodules should serve to exclude lupus vulgaris. The lesions may bear a superficial resemblance to serpiginous syphilids but here too the shiny nodules of cancer tissue should serve for recognition.

Prognosis in small basal cell carcinomas correctly treated is completely favorable If neglected or therapeutically fumbled, however the tumors give rise to great deformity particularly if the nose or eyelid is involved, and unchecked they progress to the death. Transition into squamous carcinoma is extremely unusual It may occur particularly if a lesion is inadequately treated with x rays then the prognosis is changed to that of malignancy with the possibility of metastasis.

Treatment.—Small growths used to be curetted out and acid nitrate of mercury was then applied. X rays, radium or surgery may be employed with the doses and technic as used in the treatment of squamous carcinoma (q v) Best the whole lesion is excised by a destructive physical agent such as the actual cautery Cure consists in the total extinction or incapacitation of all neoplastic cells, preferably in a manner conducive to good cosmetic results It is bad practice to use an agent without knowing accurately the destructive capabilities it possesses and their extent of action, and without accurate understanding of the gross and minute anatomy of the parts involved and the natural history of the tumor

The curative dose of x ray therapy is in the vicinity of from 4 000 to 5 000 r (Wigby and Cohen Radiol 35 70 1940) Superficial basal cell carcinomas (q v) and those of the morphea like type are not well handled by radiation, for the curative dose will cause necrosis of the dermis. No good cosmetic result was obtained by radiotherapy of any lesion over 5 cm in diameter among the 711 cases of Churchill Davidson and Johnson (BMJ 1 1465 1954)

One sees elderly patients in whom palliative radiation will yield good enough results for a few years so as to be preferable to the surgery necessary for cure

Histologic study of tissues removed from patients treated by x-ray has satisfied me that it is possible for viable tumor cells to lie enmeshed in such dense fibrotic postradiation scar that they fail to grow effectively into clinical recurrences. Injury or infection may restore succulence to the sclerotic lesion so that proliferation of tumor tissue is resumed. A case I saw of this kind wherein a result of an automobile accident was the recurrence of a seemingly cured basal cell carcinoma of a woman's nose was provocative from the medicolegal standpoint It was settled out of court in favor of the plaintiff.

BASAL CELL CARCINOMA —See Doedlas (TransPathSocLond 45 175, 1894) rodent ulcer; Krebich (AfDuS 42 323, 1898) rodent ulcer histology Dubreuill and Auché ([illegible] 1901) rodent ulcer Krompecher (BeitrPathAnat 28 1, 1900; 37 131, 1905) origin; (Der Basalzellenkrebs, Fisher, 1903) Borrmann (ZtschrKrebsfor 2 1, 1904) (Ztsch Krebsf [illegible] epithelial tests McLeod (BJD 21 249, 1909) cystic case James [illegible] Tumors [illegible] 403 1910) early stages Fordyce (J 55 1614 1910) pathology; Hertzler (Tr [illegible] 11, 1911) McDonagh (JCutD 32 [illegible]) Krompecher [illegible] New York, 1912) Loeb and Sweek (JMedRes 28 233 1913), confirming Krompecher's classification of [illegible] epitheliomas; Kyrle (AfDuS 131 [illegible] 1918–20) unusual forms and superficial; Sweitzer (J 69 179 1917), 43 cases Ketron (JCutD 37: 22, 1919) rodent ulcer and allied growths; [illegible] Cleland [illegible] (MJAustral 1 407 1920) rodent ulcer; Owen (AmPath [illegible]) Montgomery (J 82 775, 1924) Sutton (JAMA 79 [illegible] 1930), rodent ulcer; [illegible] in young men [illegible] of mucous membrane Aitken (BMJ 2 1044 1934) [illegible] neoplastic [illegible] (Radiol 26 8 1936), good photomicrographs of difference of normal and neoplastic [illegible] Newland (MJAustral 2 221 1936), 600 cases of rodent ulcer [illegible] (AmJRoe [illegible] 47: 461, 1942 [illegible] 27 1941) 5 year cure criterion Holzman and Holk [illegible] (Bri J [illegible] 11 709 1943) [illegible] lesion as somatic mutation and Juan and Oliva ([illegible]

tip of nose; Amersbach et al. (ADS 54: 119, 1946; 58: 111, 1948) cure with injections locally of spleen and liver extract; Arnold (ADS 57: 104, 1948) case suggesting sweat gland origin; Pierard and Dupont (BJD 60: 50, 1948) nodular lesions; Smithers (BMJ 1: 865, 1949) advocating cooperation of surgeons and radiologists in choosing therapy; Lennox and Wells (BritJCanc 5: 195, 1951) histologic study of 150 cases, palisade, fluid formation, whorls and pigment; Johnson et al. (PMJMC 28: 7, 9, 1953) anal cylindroma.

SUPERFICIAL.—See Gray (BJD 32: 232, 1920) generalized rodent ulcer; Little (BJD 35: 435, 1923) 7 cases of "erythematoid benign epithelioma"; Montgomery (ADS 20: 339, 1929) varieties; Wise (ADS 19: 1, 1929); Wright and Friedman (ADS 27: 76, 1933) 5 cases in psoriatics; Ba tard (BJD 47: 51, 1935) psoriasiform squamous cell lesions analogous to superficial basal cell epithelioma; Rosenberg (ADS 34: 972, 1936) case; Piper (DWchr 113: 425, 1941) progression with vegetating and ulcerative lesions, examples; Wessman and Medalia (ADS 50: 117, 1944) remarkably large solitary lesion, partly intraepidermal; Teloh and Wyerlock (APath 48: 447, 1949) histologic study of 182 specimens; Smith and Garrett (South MJ 43: 492, 1950) possibility of cure with podophyllin; Sams and Penalty (ADS 64: 142, 1951) podophyllin failure acts only superficially; Rosenberg (ADS 68: 392, 1953) found no arsenic.

XERODERMA PIGMENTOSUM

The disease may be summarized as the precocious development of sailors skin, keratoses and basal and squamous carcinomas. It appears early in life sometimes even before the end of the first year Sunlight incites and promotes its manifestations. The sites of predilection of cutaneous changes are the exposed surfaces, the face and scalp neck and forearms, and dorsal aspects of the hands. The first stage of erythroderma corresponds to the time when the child gets outdoors freely It is characterized by mottling of the skin diffuse hyperemia slight puffiness, and some roughening of the epidermis. Inflammatory irritation is provoked by actinic energy The second stage of reaction follows in the third and fourth years of life pigmentation becomes more apparent in small, freckle like spots, along with active scaling and transient hyperkeratotic lesions, while hyperemia and edema diminish. Injection of the conjunctivae becomes pronounced, and there is more or less photophobia. The third stage of degeneration is characterized by atrophic mother-of pearl like spots often permeated or margined by dilated capillaries, which appear between the pigmented areas and by warty lesions which become more numerous and pronounced, some of which in the course of months or years become carcinomas. The stages of erythema, pigmentation atrophy and tumor formation may be found side by side, the affected skin resembling an x ray burn. Pigmentation ranges from pale yellow to sepia in color By coalescence as well as by de novo appearance patches of considerable extent may become involved. Sudoral activity is somewhat lessened but the sebaceous glands are little affected. Atrophic contractures of the nose and mouth are common, and ectropion may result, occasionally with ensuing ulceration of the cornea

Etiology—Congenital predisposition is an important factor Two or more members of a family are frequently affected for instance, the 7 brothers in a family of 13 individuals reported by Rüder (quoted by Cockayne Inherited Abnormalities of the Skin, Oxford U Press, 1933) Xeroderma pigmentosum agrees in all respects with a simple recessive character due to a single gene (Cockayne)

Brothers 13 and 16 years of age presented squamous carcinomas of the lower lip; their Swedish parents were cousins (Bell and Rothnem: AmJCanc 30 574 1937) Loewenthal and Trowell (BJD 50 66, 1938) reported cases in African Negroes of related heredity with dry skins, pigmented and depigmented macules and warty growths. The inheritance is recessive and incompletely sex linked according to Macklin (ADS 34: 656 1936; 49 157 1944) and while the disease is frequently associated with consanguineous marriages, it rarely affects more than 1 child of a family

Corlett (JCutD 33 164 1915) recognized that while the condition essentially depends on inherited susceptibility it is immediately instigated by certain rays of the solar spectrum. Rothman (AfDuS 144 440 1923) discerned in his case no excess sensitivity to x rays, but ultraviolet light provoked prolonged erythema and the development of telangiectases. Marten stein (AfDuS 147: 499 1924) found the reaction to ultraviolet light enduring but otherwise not different from normal while x rays provoked pigmentation and rendered the skin less susceptible to actinic light. Per (BJD 38: 241,

1926) concluded that xeroderma pigmentosum is due to extreme sensitization of the skin to the ultraviolet rays of the sun. The congenital insufficiency of dermal resistance to actinic rays seemed to him to be dependent on the consanguinity of the parents. Photodynamic substances such as hematoporphyrin do not play any part in the pathogenesis of the disease he thought. He cited Darier's figures that 100 cases of consanguinity between parents produced progeny of whom 11 8% were xerodermatous.

Senile atrophy of the skin and sensitivity to light or increase in pigmentation from exposure to light are not necessarily primary etiologic factors, according to Montgomery and Reuter (ADS 26 256, 1932) They thought that many mild cases go unrecognized. There was no excess ultraviolet sensitivity in the patients of Greenbaum (AmJDisChild 34: 81 1927) or of MacCormac (BJD 45; 167 1933) Mathews (APath 23: 399, 1937) decided, "It remains to be proved that this form of cancer [which occurs in xeroderma pigmentosum] is a true photodynamic disease." Lynch (ADS 29; 858, 1934) found in his case especial sensitivity to radiation between 2800 to 3100 A.U Heft (ActaD-V 16: 146, 1935) observed the involved skin less sensitive to various irritants, including light than normal areas.

Pathology.—The common changes in the skin consist of atrophy of the dermis appendages and epidermis, combined with excessive formation of the horny layer and follicular increase of pigment (Councilman and Magrath JMRes 16 331 1909) Atrophy of the dermis is at the expense of the collagenous tissues the elastic fibers show a general increase and form large convoluted masses about the cutaneous appendages. In places there are horny excrescences and tumorous masses of epithelium. Becker et al. (ADS 25 915 1932) found the brown color due to a large amount of epidermal pigment, the pigmentary process appearing to be secondary to inflammatory change. The dopa reaction is intermittent as is the degree of pigmentation. The carcinomas which develop may be basal squamous or mixed in type. The warty or keratotic or horny lesions which precede them are of intergradient degrees of activity just as those are that develop from applying a carcinogen to the skin of a mouse Highly anaplastic epidermal carcinomas occurring in this disease have been sometimes erroneously interpreted as spindle-cell or giant-cell sarcomas (see p 1201 also Roentgen sarcoma, p. 1968) or other tumors.

Diagnosis.—The features of the disease comprising characteristically the tender age of the patient pigmentation, roughness and scaliness of the skin, telangiectasis and development of carcinoma together are typical, so that a mistake in diagnosis is hardly possible Freckling lentigines and systematized lentigines might be mistaken for xeroderma pigmentosum, and some authors have segregated a class of benign cases of the latter disorder on that account, erroneously in my opinion. The freckled relatives of persons affected with xeroderma pigmentosum may be heterozygotes (Siemens and Kohn quoted by Cockayne)

Treatment.—Xeroderma pigmentosum may be rapidly progressive but usually there are periods of comparative quiescence The victim may survive for many years, but ultimately he succumbs to carcinoma. One must treat keratoses as they arise and prevent exposure to the sun. Vitamin A may be given The patient is a pitiable one indeed.

See also Carcinoma, etiology light See Kaposi (Hebra and Kaposi's Diseases of the Skin, New Sydenham Soc. 3 252, 1874) "parchment skin, 4 cases; Kaposi (Path u. Therap. d. Hautkrankh., Vienna, 1883 p. 706) established name, "xeroderma pigmentosum" same patients (JCutD 2 332, 1888) 2 American cases (see White (JCutD 33: 170 1915), [illegible] (JCutD 10: 129, 1892) thirteenth American case [illegible] live at age 50] Brayton (JCutD 10: 129, 1892) [illegible] have occurred [illegible] 4 7 million; Pollitzer (JCutD 10: 132, 1892), [illegible] 164 [illegible], 1911; [illegible] Bronson (JCutD 17 572, 1899) female 8; White (BostonM&SJ [illegible] Nelson (AmJOphth [illegible] 290, 1912); Orindon (JCutD 33: 170, 394, 1915), family group [illegible] 1920) [illegible] 1919) ectropion, ulcerative keratitis; Ravdin (NYMJM 112 [illegible] 1920) [illegible] 1923) remarkabl case, Friess (Thèse de Paris, 1923, Maloine et fils, 88 pp.), pathology [illegible] Ravdin (UCutRev 20 207 1923); Rich et al. [illegible] (ADS 16: 217 1927) xerotic skin changes; Corson and Knowles (ADS [illegible] usual involvement of 1 member of affected family Joon (AfDuS [illegible] sitivity t x rays, not UV; Hering nd Harmewitz (II [illegible] brother and sister [illegible] dat , Bellisario (MJAustral 2 148, 1935) atypical in brother and sister [illegible] (ADS 43 570, 1940) Negroes; Netherton nd H bler (ADS 62: 402, 1950) mild forms [illegible] face of 3-yea -old; Anderson nd Hoex (BJD 63: 402, 1950) [illegible] Kesten and Slatkin (ADS 65: 248, 1952), Haitian boy with skin [illegible] generations [illegible] ington nd Postlethwait (AmSurg 18: 50, 1952), 13 members of 5 generations [illegible] despite plastic surgery Roncherse (ADS 66 358, 1953) case with multiple melanomas, [illegible] logically malignant, clinically benign.







Fig. 1723.—Xeroderma pigmentosum. (Dr J B. Shelmire)
Fig. 1724.—Xeroderma pigmentosum. (Dr J B. Shelmire.)
Fig. 1725.—Xeroderma pigmentosum. (Dr A. J Markley)





Fig. 1726.—Xeroderma pigmentosum: nuchal pigmentation and trophy (Dr L. Halberstaedter)

Fig. 1727—Xeroderma pigmentosum with advanced carcinomatosis in a child (Dr L. Halberstaedter)

BENIGN EPITHELIOMA AND SELF HEALING ACANTHOMAS OF THE SKIN

Self Healing of Carcinoma.—Some senile keratoses (q v) are replaced by normal epithelium and are gone. Perhaps the application of castor oil, a time-honored remedy, may abet this. The possession of neoplastic qualities by a group of epithelial cells does not necessarily signify that they will thrive The mutation hypothesis of origin of cancer aptly fits these phenomena, for keratoses resulting from x ray therapy presumably representative of cells genetically damaged are susceptible to further damage by radiation and are well treated and readily cured by the contact application of unscreened radium the action of which is superficial

Spontaneous recession of well-developed cancer has been discussed by Orth (Ztschr Krebsfor 1 399 1903-1904) and Rohdenburg (JCancRes 3: 193 1918) among others The influence of vigorous inflammation superimposed on a tumor may have conspicuous beneficial results, more likely to be palliative than curative. It was this effect of erysipelas which led to the development of Coley's serum, the earliest effort along the lines of chemotherapy; see Klauder (J 106: 201, 1936) "Cancer's self-control was the subject of a paper by Broders (MJ&Rec 121: 133 1925) in which the production of kerati by squamous carcinoma and of melanin by melanoma was cited as an example of ways in which tumor cells can be lost from progressive growth. Neoplasms have been known to heal following antisyphilitic therapy (Touraine and Duperrat: BsocfrancD 4 : 1777, 1935 AnndeD 7: 545, 1936) The cicatricial defense, sometimes partially curative of basal cell carcinoma (q v), is likewise consequential in x ray therapy of carcinoma. A spindle-cell carcinoma in a case of xeroderma pigmentosum was observed to degenerate and heal spontaneously by Follmann (KlinWchn 17 1658 1938)

Benign Epithelioma (Kerato-Acanthoma Molluscum Sebaceum Tumorlike Keratosis of Poth)—Lesions clinically indistinguishable from multiple squamous carcinomas on the face, ears, arms and thighs of a man 23 years old were observed by Smith (BJD 46 267, 1934) to heal spontaneously with the production of atrophic scars. A similar patient was seen by Dunn and Smith (BJD 46 519 1934) who described in an excised lesion *folded stratified* squamous epithelium wartlike but not apparently carcinomatous. A hemispheric nodule with a warty central crust was called molluscum sebaceum by MacCormac and Scarff (BJD 48 624 1936) who had seen several similar lesions characterized by their usually solitary appearance their rapid evolution in from 4 to 6 weeks to a maximum stage of development their preference for the midfacial region especially the nose and their conspicuous clinical simulation of rodent ulcer but absence of malignancy Tumorlike keratoses appeared on the dorsa of the hands of an elderly man who had recently been *severely sunburned and they underwent* spontaneous involution under the observation of Poth (ADS 39 228 1939) The patient of Ayres (ADS 49 83 147 1944 58 584 1948) repeatedly developed seemingly cancerous lesions on his face and many of them underwent spontaneous healing

Smith (BJD 60 315, 1948) added a third case to the 2 he had seen previously and presented them with illustration showing the deep scars left when the lesion healed. The man reported by Grzybowski (BJD 62: 310 1950) had m ltitudes of lesion resembling those of Smith cases; even th oral mucosae supported mac lar and wartlike coalescing tumors. Most of the skin lesions disappeared following the use f Vlemincks's solution. f th a d 3 so presented tumors that resembled highly differentiated squamous car inoma h tologically but he led with scars on the forearm nd face thi family wa described by Charteri (AmJRoentg 65: 459, 1951) The same disease wa familial th case described by Sommerville and Mil e (BJD 6 493 1950) In the case seen b M case of (BJD 63 151 1951) there wa a solitary lesio on a woma neck the called Wh ttle and Lyell (BJD 64 4 4 1952) were also similar to the solit ry growth called moll scum sebaceum by MacCormac and Scarff The patie t of Fliegelman a d La er (ADS 66: 333 195_) wa an old man like that of Poth with lesions of th dorsa of th hands and a im lar patient a carpenter with lesion f the forearm and arm, w xhibited t \ w a d Horton (ADS 65: 475, 1953) wh tried but failed t produce lesion b auto oculat on.

Pseudoepithelioma.—Papilloma of a un sual sort structurall resembl g ... cellular carcinoma, were found o the limbs of 3 pati t with specific re nal h ... adenopathy by Sokolow ki nd Elsenlohr (DWchn 1 1: 434 1951); local removal curative *Several case sim l t ng carcinoma* w r recorded by G Prieto and ... (Dermatologica 103 175 1951) Resembling these wa the patient of *Anderson* (BJ ...



Fig. 1728A.—Tumor-like keratoses, lesions as originally seen. (Dr Duncan O. Poth.)

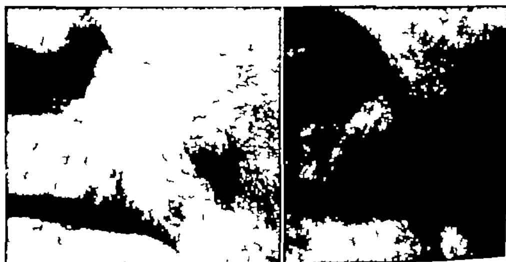


Fig. 1728B.—Complete spontaneous involution of the lesions of Fig. 1728A has taken place without treatment. The lesion on the dorsum of the right hand was removed for biopsy



Fig. 1728C.—Histologic structure of tumor-like keratosis. (Dr Duncan O. Poth.)

378 1963) a gardener with a lesion on the dorsum of the hand. This was irregular in outline and productive of scar the firm raised edge surrounding a swelling, from within which one could express cheesy pus and follicular plugs. Names more or less freely translated will serve to describe the condition further: chronic, vegetative pyodermitis (Arn MedCirugPract 34 872, 1894) excrescent, pseudoinflammatory epithelioma; carcinoid papillomatosis of the skin, and pseudoepithelioma of the skin (Arna and Sala fourteenth Internat. Med. Congress, Madrid, 1903; second Spanish Congress of Surgery 1908) See Arna (ActasDermat 2: 339 1910)



Figs. 1729A and 1729B —Kerato-acanthoma of woman cheek. A original appearance B, 5 months later untreated. (Dr John C. Belisario.)



Figs 1730A and 1730B — Kerato-acanthoma. A original appearance B 2 months after an x-ray dose f 600 r (Dr John C. Belisario.)

Etiology and Pathology—The lesions tend to occur on exposed skin, and sunlight in some instances conspicuously overdosed, plays a part in their inception. They may be solitary or multiple. The commencement according to Smith s description, is with minute reddish papules which resemble early

acne lesions but the seeming comedones are in reality horny plugs which can not be expressed They develop quickly within a few weeks or months so as to form umbilicated tumors with keratotic centers and white smooth, rolled

Fig 1731A.—Kerato-acanthoma, 6 cases in various locations on the face. (Zoon et al. Dermatologica 108 31, 1954.)

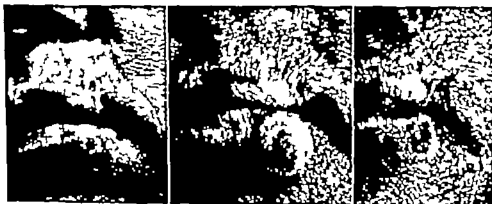


Fig 1731B.—Kerato-acanthoma, successive photographs at intervals of a few weeks, showing spontaneous healing. (Dr J J Zoon.)

edges, closely resembling squamous carcinoma. They remain stationary for a time and tend to involute spontaneously. The ulcers heal and the edges flatten out, leaving deep pitted scars, with irregular overhanging crenellated borders.

Histologically one finds a central mass of hyperkeratotic material produced by stratified squamous epithelium, complexly folded and suggestive of pseudoepitheliomatous hyperplasia. The dermis is intensely but nonspecifically inflamed and the dermo-epidermal junction may show some round-cell infiltration but invasiveness of the tumor epithelium is absent.

Treatment.—The lesions heal spontaneously or can be cured by local attack being responsive to either surgery or x ray therapy. Finley (AustralJ Dermat 2 144 1954) recommended curettage followed by cauterization.

See Fouracres and Whittick (BritJCanc 7 58, 1953), molluscum sebaceum and spontaneously healing epitheliomas are the same disease. Marshall and Findlay (SoAfrMJ 27 1[illegible], 1953) case, multiple type; Binkley and Johnson (AD 71: 66, 1955) keratoacanthoma, 2 cases and review; Ereaux et al. (AD 71 73 1955) case, multiple lesions, unusually extensive; Zoon et al. (Dermatologica 108 81 1954) 6 cases and review; New (USAFMJ 6 1719, 1955) case, multiple lesions of neck and legs, influenced by UV. Hamperl and Kalkoff (Hautarzt 5 440, 1954) histologic course during self healing. Stewart (AustralJD 2 [illegible] 1955) histologic progress of molluscum sebaceum. Allington (AD 72: 381 1955) old man with several nodules on ankle and forearm.

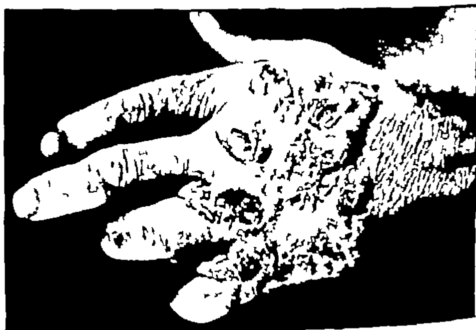


Fig 173 —A vegetative carcinoma-like lesion from which fungi were not obtained. The disease healed, undiagnosed.

MIXED NEOPLASM

Myxochondroepithelioma, a tumor that occurs commonly in the salivary glands may also be found occasionally on the palate lip cheek or gums (Abshier ADS 32 622 1935). Such a lesion is firm rounded or lobulated and slow in growth, but it is capable of considerable development. It is usually encapsulated movable and relatively asymptomatic.

Unusual locations include those rare it is true on the palm, leg arm, hand, calf or finger (Simard AmJCanc 33 18[illegible] 1938). Upper lip cases were reviewed by Ferris (Arch Path. 26 349, 1938). Brunschwig (BGO 50 407 1930) found 11 of the tongue. Basal cell carcinoma of the palate were described by Celli (ZtschrPath 47: 400 1935) but most such cases are probably of this type. Palatal lesions have been observed as large as a hen egg (D'Aunoy AmJPath 6: 137 1930). The vagina was the site of a polypoid, lobulated tumor of the size of a kid, the surface smooth, the section grayish white homogeneous and glistening (Murphy and Duffy: PSMMC 23: [illegible], 1948).

Pathology.—The tumors were defined by Harvey et al. (EdinMJ 43: [illegible]3, 1936) as undifferentiated adenoma of the serous and seromucous glands, salivary or lacrimal, of undifferentiated and

gland lobular types, prone to mucoid, autolytic, self-destructive change of their component tissues. The cells exhibit epidermoid characters both as basal cells and as squamous ones with intercellular bridges and keratinization. Certain aspects of the varied cellular appearance of these tumors led in times past to their being interpreted as endotheliomatous, cylindromatous, chondromatous, basalomatous, carcinomatous, and even sarcomatous. The tendency of the epithelium and stroma to show myxoid, hyaline, and chondroid transformation gives the tumor its special character and "mixed" designation. Histologic evidences of benignancy are undependable; their clinical behavior and recurrence must be taken into consideration.

Metastases in 21 cases were studied by Mulligan (APath 35: 357, 1943): secondary tumors from salivary gland lesions were found in lungs, pleura, liver bones, lymph nodes, kidney and spleen.

A mixed parotid tumor was induced by implanting pellets of dibenzanthracene in the parotid ducts of rabbits by Bauer and Byrne (CancRes 10 755 1950)

Treatment.—Excision is indicated, a procedure requiring unless the lesion is a small skin tumor the services of a competent surgeon, for the parotid ones are enmeshed with the facial nerve to a greater or lesser degree and tongue lesions, even when accessible cannot be identified until histologic examination is made They should not be allowed to grow, although this has been recommended, for they never become easier to cure than they are when first seen. Their progress can be extensively destructive and they are capable of infiltrating recurring and metastasizing They should be excised widely not merely enucleated (Leroux Robert RevdeStomat 40 231 1938)





Fig. 1733.—Mixed tumor of palate (Vahbler ADS 33: 622, 1936)
Fig. 1734.—Mixed tumor of parotid, uncommonly large.

Mucous Gland Tumors, rare, occur occasionally in the skin near the ear in the neck in the upper sternal area, and about the male urethra, especially along the raphe. The structure is that of simple adenoma of a mucous gland. The lesions are small and they may ooze or form vesicles which rupture (Ginsberg and Reuter: ADS 28: 52, 1933) Excision cures.

A nodule 15 mm. in diameter on the tip of the tongue was found by Gougerot and Eliascheff (ProsfrancD 43 1695 1936) to be composed of hypertrophic mucous glands, mucosal analogue of a sebaceous adenoma.

See Gaehtgens (ZischrPath 47 274, 1935) Anger Howarth (BMJ 2 988 1936) parotid Gourlay (BMJ 2 391, 1936) palate Driver (ADS 33 72, 1936), 107 palatine cases reviewed, case cured with radium needle implantation Evans (BMJ 2 1141, 1936) recurrent in soft palate; Pilcher (BMJ 1 967 1937), upper lip Loke (BMJ 1: 131, 1938) 2 lip cases in Chinese Hertzler (Surgical Pathology of Mouth and Jaws, Lippincott, 1938, p. 184); Wirth (AmJRoentg 42 846, 1939) 6 cases involving intraoral salivary glands, Robillard and Chiesma (AmJSurg 43 704, 1939) tongue Liggett (NYSJM 39 1974, 1939) palate, Lapp (MonatsOhrenh 73, 685 1939), retromolar accessory salivary glands as source of cysts and adenocarcinomas Lampe (Radiol 39 64, 1942) malignant, of tongue; Sweitzer (ADS 46 777, 1942) eyebrow Hickman (APath 37 281 1944) hand, (?) from sweat gland; Carr (BMJ 2 605, 1945) upper lip, disfiguring to a girl Cawley and Wheeler (ADS 66 349 1952) lip.

SARCOMA OF THE SKIN

Sarcoma is a malignancy primary in mesodermal cells. Sarcomas may be composed of tissues which sufficiently simulate normal tissues to permit of recognition and to these the names angiosarcoma fibrosarcoma and similar terms are applied according to the type of tissue present Others are undifferentiated and are named in accordance with the form of the cells as seen histologically spindle-cell round-cell mixed-cell or giant-cell sarcoma, with subdivision as to size of the cell large or small Malignant pigment cell tumors, probably carcinomas in fact, are called melanomas (p. 1083) Sar

comatous neoplasias of hematopoietic lymphatic and reticular tissues are discussed as lymphoblastomas. See liposarcoma, hemangioendothelioma, neurofibroma with sarcomatous degeneration, myoblastoma, and metastatic tumors.

Primary Sarcomas of the Skin provide a subject bristling with difficulties ' with respect to classification, according to MacCormac (BJD 41 401, 1929) a view which is not obsolete Unna divided them in accord with their



Fig 1735—Sarcoma of the neck, responsive to x ray therapy (Dr W L Brown)

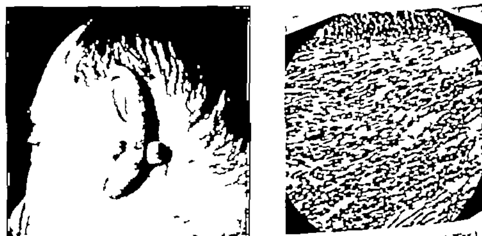


Fig. 1736—Spindle-cell sarcoma, primary in the skin of the ear (Dr Stuart Way)
Fig. 1737—Spindle-cell sarcoma, section of tumor shown in Fig 1736. (Dr Stuart Way)

solitary or multiple initial appearance the latter being subdivided into fibrosarcomas, angiosarcomas round-cell sarcomas and gummalike lesions of fine-cellular or coarsely cellular type

The round-cell sarcoma of Perrin begins with m ltiple foci small on the trunk, numbering from 30 or 40 nodules up to se eral hundred; the are situated in the derm assume a red or violet ti t as they invad the skin superficially a d progress with in crement in both ize and number and with visceral metast ses. MacCormac placed Perrin s type in his hypodermal group with multiple lesions and offered a classification as follows: (1) solitary sarcoma fibrosarcoma, polymorphous cell sarcoma of Darier and a type he himself observed which would probably now be called reticular sarcoma ( ) multiple sarcomas: dermal as represented by Un 's gummal ke forms, and hypodermal, as of Perrin's type

The classification of malignant dermal neoplasms submitted by Montgomery (J 150 1153, 1953) segregated dermatofibrosarcoma protuberans; Kaposi's melanosarcoma; hemangioendothelioma, lymphangioendothelioma and pericytoma; metastatic tumors; teratomas; and other sarcomas (including indeterminate) such as fibrosarcoma, angiosarcoma, myxosarcoma, liposarcoma, synovial sarcoma, myoblastoma and rhabdomyosarcoma. Montgomery allowed himself another pigeonhole for Miscellaneous (rarely involving the skin)." They are all rare although some kinds are rarer than others. Kaplan and Rubenfeld (AmJRoentg 37: 53, 1937) reported 74 connective tissue sarcomas, 70% of them in males, 41% affecting the lower extremity; 22 of his cases were spindle-cell sarcomas, 19 melanomas and 16 fibrosarcomas.

Sarcomas occurring in infants were described fully by Dubreuilh (AnndeD 2: 340 1911) One type is observed in the first few months, being sometimes congenital, and includes round-cell and spi dle-cell growths as well as angiosarcomas the other type described by him was lymphosarcoma.

Primary sarcoma of the skin may be described as being characterized by the occurrence of a localized, round, pea to lemon size, pinkish, reddish or purplish tumor which is likely to have developed in some pre-existing nevoid excrescence or at the site of an injury The growth may be slightly or considerably elevated above the general level of the skin either as a diffuse, infiltrated tumor or as a mushroom or pedunculated mass. Growth may be slow or rapid, usually rapid. It results in the formation of masses, usually purplish, becoming necrotic and ulcerative, sometimes fungating and granulomatous bleeding is common, noted Epstein (ADS 60 1190 1949) The lesions are usually soft and compressible or even pulsatile, their consistency differing in accordance with the amount of vascular tissue present The tumors may appear at any age in either sex. They tend to grow expansively so that they possess a sort of capsule which is invaded by tumor cells and must be excised widely if a surgical attack is to afford hope of cure.

Prognosis is best when treatment is early In Epstein s cases, mortality was high among those in whom treatment was delayed until after the duration exceeded 6 months. Of the 28 cases reported by Epstein, whose review of the literature was extensive only 2 metastasized to regional nodes. The lesion was solitary in 24, multiple in 4 The histologic types were as follows 18 fibrosarcomas, 3 angiosarcomas, 2 giant cell sarcomas, 2 neurosarcomas, and 1 each of mixed cell type rhabdomyosarcoma and myxosarcoma.

Sarcoma of the Lip.—de Cholnoky (AmJCanc 22: 548, 1934) collated 24 cases. The lesions were generally red or reddish blue smooth, located on the vermilion border and round or spindle cell in type. See Markley (J 61: 334, 1913) lower lip case; Sweitzer and Michelson (J 77: 1563 1921) small round-cell lesion of old man's lip, rapidly fatal.

Sarcoma of the Tongue.—Of the 44 cases reported prior to 1903 29 were acceptable to Fripp and Swan (Pract 70: 673, 1903) A review of 63 cases was presented by Goldstein (MedTimes 49: 158, 1921) and a more recent collation was that of Kudlich (Ztsch Krebsfor 35: 99 1931) According to Ross (BMJ 1: 54 1935) the disease is one of adult life affecting males twice as frequently as females. The tumor generally appe rs as an intraglossal mass fibrous, pinkish-white, firm and elastic, pseudoencapsulated, pushing aside the median raphe, insidious in onset, n t productive of pain in early stages, generally located in the middle or posterior third. They metastasize to the cervical nodes in 40% of the cases, also to the brain, lung and peritoneum. The pathologic types include the small and large round-cell tumors (35%) spindle-cell (25%) mixed (25%) and lymphocytic. Early surgery affords a fairly good prognosis. See Granular myoblastoma (p. 1145)

Myxosarcoma.—The tissue resembles primitive mesenchyme as in myxoma, but the st llate cells are various in size shape and nuclear staining Stout (AnnSurg 127: 706 1948) collected 142 cases, 5 resembling the 1 f Knerler and Howe (AD 72: 173 1955) a polypoid lesion of the nostril recurrent despite seemingly adequate removal.

Dermatofibrosarcoma.—Small, hard, infiltrating nodules develop in the cutis and hypoderm, and these increase in size and number slowly to form a dense bluish sclerotic plaque. After a variable but usually long period there appears on this plaque a number of projecting nodules and tumors which may be stalked, may have broad bases, or may be pedunculated or sessile (Senear et al.: ADS 17: 821, 1928) In contradistinction to the slow growth of the early fibrous nodules, these tumors enlarge rapidly often reaching the size of a small apple within a few months. They are hard, as a rule, but may soften later and vegetate particularly when the epidermis covering them becomes eroded They are whitish or purplish, and when their surface becomes eroded they may develop a tomatolike appearance. Prompt recurrence with ad-

vancing rapidity of growth is the rule after their incomplete removal. Radical excision should be done early. Most cases occur in women. A map of the distribution suggests origin in mammary ridge (Binkley ADS 40 578, 1939) a view expressed earlier by Kuznitzky in discussing the essay of Jessner (Zen-



Fig. 1738.—Dermatofibrosarcoma. (Hopper and Pinkus: AmJClinPath 20 171 1950)



Fig. 1739.—Dermatofibrosarcoma of dorsolumbar region. (Drs. Hissem and O'Donnell.)
Fig. 1740.—Fibrosarcoma of skin. (Dr O G Costa.)



Fig. 1741.—Chronic inflammatory dermatitis due to osteomyelitis of the middle phalanx, hard to differentiate from malignant tumor or specific granuloma. (Dr Stuart Day.)

tralbIIIuG 27 246 1927) I was told by Helen Curth (pers. comm., Jan., 1956) Accidental autogenous transplantation of a fibrosarcoma in performing a skin graft was reported by Harrell and Valk (AnnSurg 111 285 1940)

FIBROSARCOMA.—Pfeiffer (BeitrklinChi 44 334, 1904) 300 connective tissue tumors of belly wall; Bell (JObGyn 12 278, 1907) 10 fibrosarcomas of vulva; Klot (BeitrklinChir 123: 1, 1921) 8 cases and analysis of Pfeiffer series; Darier (AnndeD 5 545, 1924) dermatofibromes progressifs et récidivants; Hertzler (AnnSurg 84: 489 1926; Surgical Pathology of the Skin, Lippincott, 1931, p. 143), "bald-headed sarcoma" characterized by protrusion, overlying attenuated skin, attachment to skin while free beneath, almost never above the clavicle, cut surface glistening and pearly slow in growth but capable of lymphatic metastasis, composed of spindle cells in wavy bundles as if originating in adult tissue; Mattson (J 103 409, 1934) fibromyoma of vagina, 200 cases in literature, occurs from age 20 to 60 4 of 5 located on anterior wall, soft and gelatinous structure Geschickter and Lewis (AmJCanc 25 830, 1935) 8 cases of dermatofibrosarcoma, 7 in females, 3 in scars Reiter (ActaD-V 17 102, 1936) 2 cases; Sullivan (ADS 37 317, 1938) man back; Beck (AfDuS 178: 240 1938) review of 43 cases, Yamasaki (J pJD&U 43 44, 1938) 2 cases in women Touraine et al. (BsocfrancD 46 1346, 1939) man abdomen; Obermayer (ADS 39, 911, 1939) onset in birthmark on girl shoulder Meade and Brewster (AmJSurg 46: 419 1939) 41 belly wall tumors and review 180 fibromas, 63 fibrosarcomas, 61 sarcomas, 17 fibrolipomas, 6 myxofibromas, 2 myxomas, 2 endotheliomas Hausman and Tamsalz (JPediat 16: 330 1940) fibrosarcoma vulva in infant; Omens and Tobin (ADS 42: 1140 1940) case developing in scar; McClean and Pugh (JIowaMS 34 332, 1944) infant abdomen, Costa (ADS 54 432, 1946) scalp case, bibliography; Ilegnis and Payne (abs J 133 481, 1946) in scar of bite on man chest Lewis (ADS 53 146, 1946) abdominal case showing nerve trunks in fibrotic tissue; Warren (JMoMA 45 384, 1948) in boy's appendectomy scar; Saltzmann (abs J 114: 1312, 1950), 20 cases, 10 with metastases when first seen; Mopper and Pinkus (AmJClinPath 20 171 1950) 2 cases and review Gentele (ActaD-V 31 Suppl 1, 1951) 38 cases, 6 fatal, and other malignant fibroblastic tumors; Debany (ADS 63: 284 1951), man back, atypical Pack and Tabah (ASurg 62: 391 1951) 39 Memorial cases, age range 14 to 67 years, average 44, 61% males, those which special stains show to be neurofibromatous do not metastasize, reoperation needed in 3 of 39, Ebert et al. (ADS 63 189 1951) unique case involving finger Mopper (J 152 576, 1953) over 300 cases on record, trunk and back usually but can occur anywhere, not yet seen on palms or soles, 5 cases, bibliography Stafford and Ward (AnnSurg 137: 429 1953) 16 cases, 5 died, 3 with pulmonary metastases; Harris and Tablant (abs J 153 1127 1953), congenital, mastoid location, Oppenheimer et al. (Sci 118 305 1953) cellophane embedded in abdominal wall of rodents for 2 years incited sarcoma in some; Andrews (ADS 70: 683, 1954) CO_2 treatment, general anesthetic if needed; Howell (BJD 67 119, 1955) multicentric lesions of foot and thigh in Jamaican Negro; Bloom (AD 72 302, 1955) acromioclavicula nodule in a man.

Desmoid Tumors are hard fibrotic lesions occurring generally in the abdominal parieties, benign fibrous neoplasms developing in the musculo-aponeurotic structures, invading and destroying the adjacent striated muscle The new growth does not metastasize or undergo sarcomatous change. Its onset is frequently associated with a clear history of trauma. The preference for women is about 2 4 to 1. Pearman and Mayo (AnnSurg 115 114 1942) reviewed 77 abdominal cases, and Musgrove and McDonald (APath 45 513 1948) collected 34 located elsewhere. The treatment is radical surgery for recurrence is to be expected unless adequate removal is accomplished.

Neurofibrosarcoma originates in von Recklinghausen a disease only rarely Two autopsies in such cases were reported by Gray (ANeurol 22: 91, 1929) and in 1 of these the origin of tumor cells from perineural schwannian cells seemed evident. In the patient of Potter and McWhorter (AnnSurg 90: 397 1929) who reviewed the subject of malignancy supervening in neurofibromatosis a spindle-cell sarcoma of occipital location lacking demonstrable nerve fibers, recurred and eventuated in a young man s death. The benign lesions increased in number during a period of 13 years but only 1 of them became sarcomatous in a man of 60 years seen by Christie (BMJ 2 417 1940) Neurogenic sarcomas are the dangerous potentiality of deep neurofibromas, Charache (AmJSurg 41 275 1938) emphasized in a review of 19 cases, 11 of which proved fatal Of his 19 cases, 8 occurred in the thighs and 3 others in the extremities; scapular axillary and buttock tissues supported 2 each, and 1 was in the abdominal region They were encapsulated movable noninfiltrating tumors, capable of late metastasis to the lungs. Treatment is surgical

CHROMATOMA.—Tumors placed under this heading by Hertzler (Surgical Pathology of the Skin, Lippincott 1931 p 145) stand midway between the spindle cell melanomas and the neuromas. They are slowly-growing tumors which tend to local recurrence with eventual metastases by way of the lymphatics. They do not rise from a pre-existing lesion but arise in areas of skin previously normal, growing up from beneath and destroying the skin before their advancing border Their cells produce pigment at some stage in their progress in many cases. Hertzler described dermal and subdermal types of this tumor The dermal type begins as isolated tumor which seem as if set into the skin. It is found sometimes on the trunk, oftener about the shoulders and on the extremities. The subdermal type, more numerous, first appears as an isolated tumor chiefly of the lower extremity and it invades the epidermis only secondarily A primary nodule

of the dermal type enlarges without destroying the skin, attaining the size of a hickory nut or even a walnut without other change. Other nodules may form in the neighborhood, and sooner or later lymphatic metastasis takes place. Often the disease remains localized for many years, even following successive removals, before metastasizing. Hertzler's chromoma would likely be diagnosed as a spindle-cell neurosarcoma by a surgical pathologist at present, Helwig told me. I call attention to Hertzler's acumen, for he published in 1931 the statement that he suspected both the melanomas and these chromomas will ultimately be brought into the neurogenic fold.

See Schmidt (ADS 32 626, 1935) chromoma, girl forearm, not identified as such; Montgomery (ADS 40 1044, 1939), chromoma, ankle of Negress, not identified as such; Wernsdörfer (DWchn 112 147 1941) chromoma, not identified as such; Krause and Hand (ADS 47 595, 1943) spindle-cell lesion of boy' scalp.

Roentgen Sarcoma.—Smooth hard, eventually fungating lesions, recurrent and malignant have been reported to occur following x ray injury. The tissue is highly cellular, and the cells are generally spindle-shaped or polymorphous. These lesions are in fact probably spindle-cell carcinomas (q.v.). Cases involving the arm and knee regions were reported by Beck (MünchMWchn 69 623 1922) subsequent to radiation therapy of cutaneous tuberculosis the usual history; see Allen (BeitrklinChir 143: 567 1928); Holtknecht (BeitrklinChir 14 : 671 1929); Mulsow (J 96 2030 1931); Deutcke (BeitrklinChir 169: 214, 1939). The lesion followed a burn suffered 15 years previously on the cheek of a woman seen by Burgess (ADS 41: 407 1940) recurred repeatedly and invaded the jaw.

Etiology and Pathology.—The role of trauma and irritation has of course been postulated (Bradley BMJ 1 599 1929) but the cause is little understood. Some chemical agents, carcinogenic when applied to epithelium, provoke sarcoma when introduced beneath the skin benzpyrene injected into the spleens of 96 mice resulted in the development of monocytic leukemia in 9 instances and other sarcomas in 4 reported Furth et al. (AmJCanc 31 276, 1937). These authors succeeded in inoculating leukemia by the transference of a single cell. Dibenzanthracene sarcoma induced in the mouse seemed not capable of propagation with cell free filtrates (McDonald and Woodhouse JPathBact 47 615 1938).

The induction of fowl sarcoma was studied by Besredka and Gross (An InstPasteur 60: 465 1938) who found that birds in which induced tumors receded were thereafter immune. In rats the implantation of estrogenic substances led to the development of sarcoma at that site (Gardner et al.: APath 21 504, 1936; see Edit J 106 1990, 1936). Methylcholanthrene-induced sarcomas in rats, readily transplantable were minced, mixed with alcohol and extracted, and the extract, injected into similar tumors, brought about their dissolution by lysis the cured rats were subjected to attempted transplantation with the same tumor but proved to be immune, although their immunity was not transmitted to their offspring (Aptekman et al.: JImmunol 5 : 77 1946; 60: 51[illegible] 1948).

Grading of Malignancy of Fibrosarcomas was undertaken by Broders (SGO 69 267 1939) in a study of 148 primary solitary lesions. He judged that fibrogenic and cellular spindle-cell sarcomas formed distinct groups. The former appeared in older patients, the latter were more malignant. The degree of malignancy seemed to vary with the number of mitotic figures and tumor giant cells.

Treatment.—The tumors differ greatly in their radiosensitivity and are generally to be treated by radical surgical attack if metastases are not already demonstrable. Surgery if adequate may cure even after failure of an initial effort (Bigger SouthMJ 40 392, 1947). Recurrence increases the danger of metastasis, for this occurred in only 6 primary cases but in 28 of those which had already locally recurred according to Warren and Sommers (ASurg 33 425 1936). Chemotherapy discussed under Lymphoblastoma, may perhaps have something to offer in radioresistant inoperable cases. It is worth remembering that Coley (SGO 13 174 1911) using mixed toxins of erysipelas streptococci and *B prodigiosus* was able to report arrests of 5 years or more in 31 of 65 cases.

MULTIPLE HEMORRHAGIC SARCOMA OF KAPOSI

Symptoms.—Several lesions usually develop simultaneously the limbs being the sites of predilection. The early manifestations may take the form of ill-defined doughy infiltrated plaques, or collections of several firm, bean to pea size reddish or purplish nodules often with accompanying telangiectases. The course of these lesions is erratic they may persist unchanged for months, or ulcerate or disappear spontaneously. New growths constantly spring up however and in a few months the involved parts, especially the

legs, become greatly enlarged, the skin being rugous and nodular, and bluish or purple in hue. Symptoms of the skin manifestations are usually slight, although nodules and plaques may be tender or pruritic. Visceral involvement may cause hemorrhage, diarrhea and other symptoms. Necropsies have shown that the disease may affect almost every organ of the body





Fig. 1742.—Kaposi' sarcoma. (Dr Howard Fox.)
Figs. 1743 and 1744.—Kaposi sarcoma, lesions of feet. (Dr L. Halberstaedter)



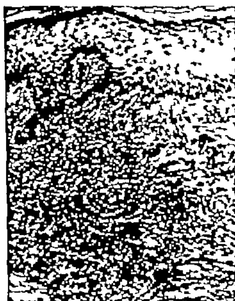


Fig. 1745.—Kaposi' sarcoma. (Dr Howard Fox.)
Fig 1746.—Kaposi sarcoma, newly formed vessels with endothelial linings, edema and pigment granules. (Dr Harold N. Cole.)

The course of sarcoma of Kaposi (AfDuS 4 265 1872) is ordinarily slow and steadily or intermittently progressive. It may be rapidly progressive. The duration varies from 1 to 25 years. Death generally is attributable to hemorrhage and progressive emaciation secondary to extensive visceral involve-

ment. In spite of the fact that spontaneous cures and cures following therapy have been reported (Lang and Haslhofer ZtschrKrebsfor 42 1 1935) casting doubt on the cancerous causation popularly hypothesized, the fact remains that the average expectancy of life is between 5 and 10 years. Hemorrhage from a visceral metastasis caused death in a patient of Aergerter and Peale (APath 34 413 1942) Obstruction of the gut was what finally killed the patient of Riordan and Rottino (ADS 60 973 1949) a man with oropharyngeal lesions of over 2 year duration.

The eruption in Kaposi s sarcoma is characterized by nodules and plaques of a bluish red or reddish brown color as described by MacKee and Cipollaro (AmJCanc 26 1 1936) whom I quote extensively here The initial lesion may be either a nodule or a plaque, more frequently the latter Usually both are present but occasionally the eruption consists of one or the other alone or one type may predominate The nodules are variously from a millimeter to a centimeter or so in diameter There may be only two or three lesions or they may be numerous Babès having counted 450 in one patient The lesions may be discrete coalescent and even conglomerate Occasionally they are closely crowded together forming large and small masses or tumors They are firm often shiny rarely translucent, and generally distinctly demarcated. They may be round oval or irregular At first there may be only slight infiltration, which becomes more pronounced as the lesion grows older Occasionally a combination of infiltrating plaques and discrete nodules produces an extensive hard swelling so that the involved hands, feet, arms or legs may attain the proportions of elephantiasis.

The site of predilection is the extremities eruption is likely to be unilateral at first but becomes bilateral during the course of the disease with a tendency toward symmetry Occasionally it is generalized. Cases remaining localized for a time occur; that of Webster (ADS 30 363 1934) was limited to the dorsum of one hand. The first cutaneous lesions occur, as a rule, on the extremities, occasionally in other locations In cases on record the initial efflorescences were on the cheeks and nose and Wise (MedRec 88 513 1915) had a patient in whom the earliest and most objectionable lesions were there

The eruption evolves slowly as a rule and the affection is progressive Old lesions often undergo spontaneous involution, leaving atrophy depressed scars and pigmentation At the same time new nodules or plaques appear Grouping of lesions, and the development of nodules at the periphery of older lesions, may produce a configuration suggestive of syphilis. In the vast majority of cases early lesions are superficial and are located in the skin, but nodules have been known to originate in the hypoderm and to invade the skin later from beneath.

Unusual cutaneous features are glistening nodules which resemble thick walled vesicles and bullae as in cases of Wise and Eller (ADS [illegible] 625 1923) and Dillard and Weidman (ADS 11 [illegible]03 1925) Lymphatic cysts have occurred, such as are seen in lymphangioma circumscriptum. These are the size of a pea or a cherry The color may be pinkish, brownish, or bluish. Lesions of a verrucous character occur Telangiectases may at times be visible in the nodules and plaques and even in apparently normal skin Petechiae and purpura are occasionally encountered. The occurrence of localized and widespread purpura in which nodules and plaques developed has been recorded by a number of observers Cases with nodules distributed along the deep [illegible] have been reported as was that of Saphier (AfDuS 118: 671 1913) where there was sarcomatous thickening of vessels and nerves. The lymph nodes are often palpable due either solely to inflammation or to proved Kaposi sarcoma. Ewing (AmJCanc [illegible] 1936) thought that these may be true embolic metastases Wise and others have reported enlarged tonsils, while Dillard and Weidman demonstrated the disease in the lymphoid tissue in the base of the tongue and nasopharynx. A case of Kaposi sarcoma combined with mycosis fungoides and a blood picture of lymphatic leukemia was reported by Lane and Greenwood (ADS [illegible] 613, 1933) Early there is hemorrhage from the cutaneous orifices, particularly the nose mouth and throat; these parts may exhibit nodules or plaques of infiltration.

It has been thought that the extracutaneous lesions were metastatic. It is likely that such foci are primary that there is no metastasis. While the first manifestations of the affection [illegible] ordinarily in the skin there is evidence that other parts become affected early or simultaneously and even that the disease may begin in the [illegible]. [illegible] had a patient who complained of intestinal symptoms before there were any lesions on the [illegible]; other skin nodules of Kaposi sarcoma were found in the large and small intestines and other viscera. Involvement of internal organs may result in hemorrhage cough, diarrhea and various other clinical indications but these are likely to be almost ignored, or misinterpreted. There may be no certainty of visceral complication until necropsy.

Necropsies in [illegible] cases have shown that the disease may affect almost every organ of the body Dorffel (ADS [illegible] 608 1932) reviewing 302 cases, found that, after the skin,

the gastrointestinal tract including all portions from the mouth to the rectum was the organ most frequently involved. Next in order were the liver lungs and retroperitoneal and mesenteric lymph nodes. The spleen, pancreas, kidneys, suprarenal glands, peritoneum, testes, trachea, pleura and heart are less frequently but not rarely affected. Lesions have been found in bones, tonsils, tongue, brain and peripheral nerves.

Etiology and Pathology—The cause is unknown. Extensive reviews have appeared by Dörffel (1932) and Choisser and Ramsey (AmJPath 15 155 1939) among whose 600 cases were 2 primary in the right heart and lacking skin lesions. Visceral metastases occurred in about 10%; peak incidence was in the fifth, sixth and seventh decades, males were affected about 15 times as commonly as females no parasitic etiologic agent has ever been proved to be significant, although the occasional spontaneous regressions are curious if the lesion is blastomatous hematopoietic variations have ranged from lympho-



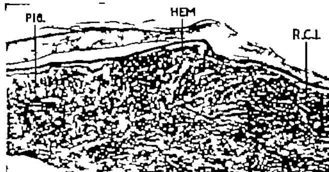


Fig. 1747—Kaposi sarcoma, lesion on tip of nose (Dr Fred Wise.)

Fig. 1748—Kaposi sarcoma. Old hyperkeratotic lesion from foot, showing horizontal trend of ectatic spaces, which indicates that they are lymphatic, not blood vascular for they follow the disposition of the collagen bundles. *PIG HEM* and *RCI* are regions, respectively of pigmentation, hemorrhage and round cell infiltration. (Dr Frederick Weidman.)



Fig 1749—Kaposi sarcoma, lesions of gut. (Riordan ADS 60 975, 1949)

cytosis to frank lymphatic leukemia and mycosis fungoides and theories of origin have ranged through infectious granuloma infection with neoplastic changes supervening neoplasia and reticuloendothelial hyperplasia Choisser and Ramsey (SouthMJ 33 392, 1940) favored the neoplastic theory considering the lesion an angioreticuloendothelioma.

Visceral lesions, hepatic, renal, intestinal and mediastinal, especially concerned Tedeschi et al. (APath 53: 335, 194) who attributed the variety of manifestations to the multiple developmental potentialities of the reticulum cell as the basic unit of the growth. Sachs et al. (JID 8 317 1947) thought of Kaposi disease as a systemic angiosarcomatosis and exhibited color plates of the histologic findings of new blood vessels lymphangioendothelium, connective tissue hyperplasia, hemorrhage and cellular infiltration comprising small round cells wandering connective tissue elements, plasma cells, angioblasts, spindle cells, and fibroblasts. Any of these features may predominate so that one section may simulate angioma, granuloma, inflammation or malignant sarcoma but vascular hyperplasia, hemorrhage angioblasts and

spindle cells are constant. Pautrier and Diss (BJD 41: 93 1929) believed that the sarcomatosis, or better the "pseudosarcomatosis" of Kaposi, stands in the same relation to the vascular system that Recklinghausen's disease does to nervous tissue. Dörffel (1932) believed that sarcoma of Kaposi is a disease of the reticuloendothelial system, an opinion with which Ewing (1936) disagreed. The patient of Cole and Crump (ADS 1: 283, 1920) had also leukemia.

The spindle cells grown in tissue cultures of explants by Becker and Thatcher (JID 1: 379, 1938) were not fibroblasts. When the cultivated cells were transplanted into the patient, typical Kaposi's sarcoma evolved at the surgically traumatized site the graft apparently taking.

Pigment seems to result from the disintegration of blood from capillary hemorrhages. The lesions beginning in the skin simulate angiomas, with proliferation and dilation of the capillaries (*Gilchrist and Ketron: JCutD 34 429 1916*). *This is followed by proliferation* of the interstitial connective tissue and *endothelium*. The infiltrations resemble in some areas young connective tissue, in other areas, sarcoma. As the lesions grow older they assume a more fibrous aspect and may undergo involution. The intertwining of capillaries and fibrosarcoma like cells is entirely characteristic, according to Stout (JMeMA 44: 273, 1949), who noted that the course is more likely to be rapid in young individuals.

Secondary anemia is fairly common and may be severe. The total and differential leukocyte counts are usually normal or approximately so. Eosinophilia of 3 to 9% occurs fairly frequently and monocytosis of 8 to 25% is usual (MacKee and Apollano).

The patient of Denser and Leopold (ADS 37 85, 1938) was a boy only 4 years old; autopsy was performed. Familial incidence, 3 brothers and a nephew being involved, was reported by Greco (*SemMéd 43: 1761, 1936*). The patients of Ellis (ADS 30 706, 1934) and Loewenthal (ADS 37 972, 1938) were Negroes.

Greco et al. (SemMéd 2 229 1938) attributed familial cases to transmissible infection *with Cryptococcus hematicus, a budding intracellular parasite of the red* blood cells, which they saw in 9 cases. The organism apparently resembles *Bartonella* (see Verruga peruana). It was on this basis that penicillin was given in large doses, with benefit claimed by Pierini and Grinspan (abs YBD 1949 p 75). This was not confirmed in 6 cases so treated by Waters (JID 16: 193 1951).

Diagnostic Clinical Features of Kaposi's Sarcoma

(Ronchese and Kern PostgradMed 14 101, 1953)

More commonly occurs in males	Lesions painless
Greatest incidence in the six and seventh decades of life	Ulceration uncommon
Predominant involvement of extremities	Edema of an extremity common
Symmetry	Residual atrophy and pigmentation of lesions that in-olut spontaneously
Bluish, bluish red or reddish brown nodules and plaques	Slow progress without change, until late, in the patient's general condition

Treatment.—X ray *therapy proves* helpful, small doses being sufficient to give much relief at first (Newman ADS 47 293 1943) and radium too, may be used. Recovery has apparently occasionally followed hypodermic injections of sodium cacodylate, although such records are old ones of patients whose disease may have been sarcoid. Results in cases treated at Radiumhemmet solely by irradiation (Hansson abs ADS 44 1119 1941) appeared to justify hopeful prognosis, for only 7 of 23 died, and their deaths were not certainly due to Kaposi's disease. One might hope for benefit from some chemotherapeutic agent although nitrogen mustard yielded no benefit in a case of Osborne et al. (J 135 1123 1947). Penicillin is of no avail.

See Oulmann (JCutD 36, 198, 1918) case, leg in ointment simulating scleroderma; Scholtz (UCutRev 24 385 1920); Ormsby and Mitchell (ADS 3 447 1921) ... Pack (... great bites of legs; Frost (ADS 3 186, 1921) case, male, widespread lesions; (Handbuch, Springer 11 14 683, 1931) failure of inoculation with Berkefeld filtrates; Kren (... right upper ex... 3 331 1932) exhaustive to date; Webster (ADS 30 363, 1934), limited to lymph nodes and skin ... tremity; Cappelli (AtDuS 181 12, 1940) fibrohemangioma of lymph nodes ... Jacobsen (abs J 119 ... resembling Kaposi; Hailey (MedTimes 69 12, 1941, case, male, 71; Jacobsen (... AmJ ... 1942) case, woman, 66, face lesions destroyed parts of skull; Thiers et al. (ADS ... 1953), guinea pig heterotranspla ts failed to transmit disease; Ronchese and Kern (ADS 69 ... 1954) ... 342, 1954) osseous lesions in case resembling hemangioma; Pack et al. (ADS 69 ... YBD 1954, p 83), favorable concurrence of lymphoblastoma in 3 cases; Jaeger and Gelser (abs YBD 1951, ... results of penicillin 600,000 units daily for 30 days; Coburn and Morgan (AD 71 419 1955), histology of early lesions.

DISEASES PRESUMABLY SARCOMATOUS OF THE HEMATOPOIETIC SYSTEM AS SEEN IN THE SKIN

LYMPHOBLASTOMAS

Introduction.— The origin of the leukocytes is thought to be in the primitive reticulum cells, from which maturative steps lead to 3 distinctively different kinds of cells, lymphoblasts myeloblasts, monoblasts, from which in turn are formed lymphocytes, myelocytes and monocytes, wrote Andrews (*Diseases of Skin, Saunders, 1946*)

Some hematologists believe that in addition, cells of the reticuloendothelial system which are derived directly from this syncytium, retain their hematopoietic ability to produce cells of the lymphoid myeloid or monocytic series. Two kinds of hematopoietic diseases result from hyperplasias of these cells. Leukemia is a growth of these cells in the circulating blood with a decrease in the maturation of the cells, being designated lymphatic leukemia, myelogenous leukemia or monocytic leukemia according to the variety of proliferation. Another form of hematopoietic disease is characterized by the proliferation of these cells within the tissues without leukemic changes in the blood. To the latter group the terms aleukemic leukemia, aleukemic myelosis and aleukemic reticulosis (or aleukemic reticuloendotheliosis) are applied. As combinations of all of the previously mentioned forms occur it is natural that some confusion exists in the classification of these processes. The term lymphoblastoma includes several diseases of lymphatic origin, but myeloid and monocytic leukemia, reticuloendotheliosis and mycosis fungoides are not properly included in it. In a small group of cases of leukemia, blood smears may show unusual cells which resemble not only monocytes, but also lymphocytes, myeloblasts, plasma cells and reticuloendothelial cells. To this disorder Ewald gave the name leukemic reticuloendotheliosis, which term is also applied to monocytic leukemia. The former is regarded by many as a subleukemic form of the latter Likewise aleukemic reticuloendotheliosis is regarded as the aleukemic manifestation of monocytic leukemia. The present tendency is to emphasize the genetic relationship of these various diseases, but there are essential differences as well as similarities. Cases are reported in which at one phase of the disease the clinical and hematologic picture is of lymphatic leukemia, at another stage that of mycosis fungoides or at some other stage some other type of lymphoblastoma. In other cases there have been simultaneous developments of leukemia and reticuloendothelial reactions, such as in Kaposi s hemorrhagic sarcoma. Infiltration of the skin with hyperplastic hematopoietic tissue occurs most frequently in the affections commonly designated lymphatic leukemia, mycosis fungoides and lymphosarcoma, less often in myelogenous or monocytic leukemia, Hodgkin s disease and in other members of the hematopoietic group of diseases.

Tumors involving the hematopoietic tissues may affect the skin primarily or secondarily Their component cells may, like sarcomas (q v) of other tissues, resemble a normal type of cell with sufficient similarity to justify specific tissue diagnoses, such as lymphocytic, myeloid or monocytic processes. The cells of the tumors may remain fixed in their sites of proliferation, or they may circulate and the diagnosis is thus to be qualified as aleukemic or leukemic. A process at one time aleukemic may become leukemic, or vice versa or the extent of leukemia may vary greatly during the course of the disease.

Lymphosarcoma.—It is debatable whether the processes designated as leukemia, aleukemic leukemia, lymphosarcoma, Hodgkin s disease mycosis fungoides and the like are in fact sarcomas, but Warthin (AnnSurg 93 153 1931) argued There is no inflammation in these neoplasms, all the patients are dead, the course is inevitably fatal they spread by infiltration, they have all the characteristics of neoplastic overgrowth and none of an infectious process. Keim (ADS 19 533 1929) concluded, after a study of many cases of leukemia mycosis fungoides, lymphosarcoma and Hodgkin's disease, that these disorders are genetically related pathologically and might profitably be grouped under one heading 'lymphoblastoma.

It is for those who defend the theory of infectious etiology to demonstrate transmission of an i fectious agent. Richter and MacDowell (JExperM 57: 1, 1933) were convinced that experimental leukemia in mice has not been transmitted without the introduction of living cells. Furth et al. (AmJCanc 31 2'6, 1937) transplanted the disease in mice with the transfer of 1 cell. F rth and Furth (AmJCanc 34: 169 1938) injected the carcinogen, benzpyrene into spleens of 96 mice, and 9 monocytic leukemias and 4 other sarcomas resulted. The lymphoblastomagenic power of other chemical substances is further attested by experiments of Bress nd Marble (AmJCanc 37: 45, 1939): in a strain of mice with a 3% standard incidence of nontransplantable lymphomatosis, painting the skins with tar increased the incidence to 50% and the course became more rapid.

There is ample evidence, believed Laws (CancRes 14: 695, 1954) to support the concept that leukemia is a neoplastic disease and, like other neoplasms, represent a heterogeneous group of diseases characterized by excessive proliferation of cells with imperfect maturation. The essential transformation is restricted to the cell. Though generally, the morphologic characters of leukemic cells resemble those of immature cells biologically they represent a new race of cells, and, when grown in vitro, they retain their characteristics and autonomy indefinitely

The coincidence of histoplasmosis and lymphoblastoma in 4 cases reported by Ca... and Curtis (JID 11: 443, 1948) was remarkable, and the relationship was not explained, nor was too much hypothesized about it.

*It has been argued that individual types exist and that to lump the lot as lympho*blastoma might, but does not necessarily lead to overlooking well-defined clinical and pathologic distinctions. Perhaps the differences are of the same order as those that distinguish squamous carcinoma *from* basal cell and other types of epidermal neoplasia, lesions which show significant differences with regard to age incidence, site of predilection, degree of malignancy rate of progression, and cytologic arrangement and detail but which are all epitheliomas. When one names a *disease*, for example, acute lymphatic leukemia, his inability to distinguish a particular leukemia cell from its normal analogue does not confuse him in his *knowledge* that they behave differently In association with differences of cell type and behavior there are various distinguishable clinical pictures.

In 43 cases representing a variety of lymphosarcomas studied by Isaacs (AnnI tM 11 657 1937) leukemia developed in 10 males and 5 females; he called this "lymphosarcoma-cell leukemia." Epstein and MacEachern (ArchIntM 60 867 1937) thought the presence or absence of leukemia a matter of little moment—a fact not to be refuted from the clinical and actuarial standpoints.

Histogenesis and Classification.— The lymph node consists of a fibrous tissue capsule with its trabecular prolongations and an internal scaffolding of anastomosing reticulate cells with their associated reticulum fibrils, wrote Dawson et al. (EdinMJ 44 645 1937) The essentially lymphocytic tissue consisting of peripheral nodules (germinal centres) and anastomosing pulp cords running through the medulla to the hilum, is developed from the reticulate cells and occupies the reticulate meshwork. It seems to us that undifferentiated mesenchyme must be almost universally existent in the loose areolar myeloid sinusoid and lymphoid tissue of the adult body We should prefer to denominate this tissue and its cells mesenchymal rather than reticuloendothelial These progenitor cells, though showing a determination to the production of specific tissue in certain localities, e.g., the lymphoblast of the germinal centre may still be regarded as mesenchymal tissue persisting in the adult. This view simplifies the distinction for lymphoid tissue, between lymphoblast reticulum cell, endothelium, macrophage and lymphocyte. The lymphosarcoma of smaller or larger cell type arises from an undifferentiated or little differentiated mesenchymal cell which constitutes in adult life the stem-cell of lymphoid tissue and has, in situ, the productive potentialities of reticuloblast fibroblast and lymphoblast "

The classification of Robb-Smith (JPathBact 47 457 1938) is worthy of careful study see Reticular sarcoma. Krumbhaar (J 106 286 1936) listed myelogenous lymphogenous and reticulogenous neoplasias as follows

	MYELOGENOUS	LYMPHOGENOUS	RETICULAR
Tissue hyperplasia and leukemia	Acute or chronic myelogenous leukemia (leukemic myelosis)	Acute or chronic lymphocytic leukemia (leukemic lymphadenosis)	Monoblastic leukemia (leukemic reticulosis) monocytic leukemia
Aleukemic variety of hyperplasia	Acute chronic aleukemic myelosis	Acute or chronic aleukemic lymphadenosis	Aleukemic reticulosis
Malignant tissue changes only	Myelogenous myeloma aleukemic myelochloroma	Lymphosarcoma; lymphoid myeloma plasma cell myeloma; lymphochloroma	Reticulum-cell (retothelial) sarcoma

The classification of Gall and Mallory (AmJPath 18 381 1942) who pointed out that the designation malignant lymphoma has the advantage of being noncommittal as to pathogenesis, attempted to integrate cytologic ara-

tomical, and clinical aspects of these diseases. Their survey of 546 adequately documented cases enabled them to recognize that the cytologic type is remarkably constant over a period of time. A classification based, however on distribution of lesions or on the presence or absence of leukemia, proved unstable The *mass of their material excluding certain exceptional cases, fell into* 7 categories stem cell lymphoma, clasmatocytic lymphoma, lymphoblastic lymphoma lymphocytic lymphoma Hodgkin s lymphoma Hodgkin s sarcoma, and follicular lymphoma

Their stem cell lymphoma included cases described by others as reticular sarcoma. Thei clasmatocyt c lymphoma included those cases in which differentiation of cells takes place in the direction of tissue phagocytes. The distinction of tumors of the lymphocyt series into lymphoblastic and lymphocytic depended on whether there was predominance of immature or mat re cell types. They unhesitatingly placed follicular lymphoma among the malignant rather than inflammatory tumors. The value of this classification was put to the test of clinical correlation. Although considerable overlapping was observed, suffi ciently constant differences were found in the age of onset, duration of the disease maximal frequency of involvement of various organs and tissues, tendency to localization or generalization the development of leukemia and the degree of radiosensitivity to delineate a series of recognizably diff rent clinical syndromes.

A sliding scale with primitive mese chyme at one end and fully differentiated tissues at the the was used in the prognostication of all of their tumors of the mesenchymal group. The nearer the struct re of the tumor approached the indifferent mese chyme, the more rapid was its course and the more dismal its prognosis. See also Weidm n and Custer (in YBD 1937, p. 326)

An object of this classification is to point out that the so-called stem cell sarcoma resembles undiffere tiated mesenchyme (Sahyoun et al.: ValMonth 76: 620 1949) Any tumor included under the mesenchymal heading when it becomes anaplastic may develop nto a cell type which m rphologically approaches primitive mesenchyme, regardless of wh the it origin be lipid, fibroblastic, myeloid or lymphoid.

Following histologic study of some 1,300 tumors Custer and Bernhard (AmJMedSci 216: 625, 1948) co cluded that som cases show one type of structure, such as Hodgkin's disease in one part and lymphosarcoma in anothe part, and reticulum cell sarcoma and lymphosarcoma may be so associated. They thought that rigid subclassification of the lymphomas is artificial, reticul r diseases being a si gle neoplastic entity with a number of variants.

PSEUDOLEUKEMIA was a term formerly used in a limited way for Hodgkin s disease. The term became pplicable to the het rogeneous group of conditions resembling one an other in manifesting enlarged lymph nodes and aleukemic blood findings, including leukemic lymphadenosis, aleukemic myelosis, Hodgkin's disease, retothelial sarcoma, multiple myeloma, and syphili and tuberculosis of lymph nodes. The word is of historic interest onl

Nomenclature wa clarified by the essay of Forkner (AI t M 60: 682, 1937)

Skin Lesions.—The study of 445 cases by Epstein and MacEachern (AInt M 60 867 1937) showed that the skin was involved as follows

	No. of cases	Specific lesions	Ids
Hodgkin's disease	156	12	51
Lymphosarcoma	122	17	23
Myeloid leukemia	90	5	47
Lymphatic leukemia	60	5	27
Monocytic leukemia	4		1
Plasma cell leukemia	1	1	0
Reticulo-endotheliosis	1	0	0

	Hodgkin's disease	Lympho-sarcoma	Myeloid leukemia	Lymphatic leukemia	Acute leukemia	Monocytic leukemia
No. of cases	156	122	90	60	6	4
Petechiae	4	4	47	15	2	1
Pigmentation	16	2	2	1	0	0
Stomatitis	1	3	11	4	1	0
Pruritus	12	4	0	2	0	0
Maculopapules	1	0	3	1	0	0
Herpes zoster	4	1	1	1	0	0
Bullae vesicles	3	1		0	0	0
Furunculosis	0	1		1	0	0
Lichenoid papules	0	1	0	1	0	0
Urticaria	1	0	0	0	0	0
Herpes simplex	1	3	0	0	0	0

There is no sharp dividing line between the so-called exanthems and true tumors, Gates (ADS 37 1015, 1938) found. Leukemia as *tumors with circulating metastases* and lymphoma' as tumors which arise in discrete locations she thought cannot be differentiated as to cutaneous lesions clinically or pathologically Mycosis fungoides she considered a type of leukemia or lymphoma with predominating skin tumors. The skin tumors seem to be the result of chance location of diffusely disseminating cells. In some cases, sites of injections and surgical incisions have become infiltrated with leukemic tissue noted Cleland (BMJ 2 1191 1935) who attributed such lesions to metastasis.

Zosteriform distribution of lesions in leukemia cutis is seen (Barney: ADS 37 238 1938) Keim (ADS 10 579 1924) believed that zone determines the localization of aggregates of cells previously infiltrating in invisible quantities.

Nomland (JIowaMS 27 25 1937) showed cases illustrative of general pruritus most commonly occurring in Hodgkin s disease, of exfoliative dermatitis, in chronic lymphatic leukemia of local leukemic deposits and of purpuric lesions with stomatitis in acute leukemias, especially of the myeloid type.

See Nékám (Ueber di Leukaemischen Erkrankungen der Haut, Voss, Leipzig, 1899); Minot and Isaacs (J 86: 1184, 1265, 1926), 476 cases, 68% males, Hodgkin's maximum incidence at age 26-24 next peak at age 35-39 with diseases other than Hodgkin s, average expectancy 2.0 years not lengthened but more comfortable with x ray therapy, Desjardins et al (AmJRoentg 36, 169 1936), complications Kiszery et al (ADS 36 910 1937), sternal puncture technic and results, Gaté and Cuilleret (JMédLyon 18 299 1937), polymorphism and origin in parapsoriasis, Forkner (Leukemia and Allied Disorders, Macmillan, 1938, 333 pp), monograph with extended bibliography Goldsmith (BJD 56 107 1944), reticulo-endothelial system and tumors thereof showing variability and polymorphism Robb-Smith (BJD 56 111, 1944) reticular tissue and reticuloblastoma in the skin.

SKIN LESIONS IN CIRCULATING CELL BLASTOMAS OF THE HEMATOPOIETIC SYSTEM

The lesions of leukemia in the skin may be clinically indistinguishable from those occurring in purpura, prurigo and other cutaneous disorders, or they may be typically lymphadenotic in character Purpuric skin manifestations may or may not include formation of bullae, and may involve the mucous membranes as well as the skin. Pigmentation may be Addisonian as a result of leukemic damage of chromaffin tissue (Symmers AmJMedSci 167 157 1924) The patient with leukemia may have also any other skin disease and often suffers from secondary infection and hypoproteinemia. There are many ways in which lymphoblastoma may influence the skin indirectly

The 3 types of specific skin lesions comprise (1) leukemids, (2) erythrodermic infiltration of the skin with tumor cells, and (3) circumscribed tumor formation.

Leukemic tumors in the skin vary in size from a few millimeters to several centimeters and usually occur in large numbers, though they are occasionally solitary wrote Gates (ADS 37: 1015 1938): In the most common form the eruption starts with small papules, and these increase slowly in size and number Erythematous macules and slightly indurated plaques are not uncommon. In many cases diffuse though not completely generalized swelling of the skin is associated with discrete cutaneous tumors. Extensive ulceration may occur and the diagnosis of mycosis fungoides is occasionally made Some of the tumors have a moist eczematous appearance. The color of the tumor changes from bright red to deep purple to dusky brown. Though the tumors are usually considered of grave prognostic import some of them occur a year or more before death. There are no characteristics of cutaneous tumors in leukemia which would distinguish them from other metastatic cutaneous tumors.

"A special form of infiltration is seen in leukaemia cutis universalis, which is an exaggerated generalized form of erythroderma due to the infiltration of tumor cells. It occurs most often in lymphatic leukemia and is characterized by a thickening of the entire skin, accentuating all body folds and producing a leonine countenance The swelling may be of light or dark color is usually

symmetrical and causes intense itching The surface is scaly or eczematoid. In the case reported by Ketron and Gay (ADS 7 176 1923) there was extensive wartlike hypertrophy of the skin of the ankles.

Circumscribed lesions may consist of macular or slightly elevated patches, or of oval topped, pea to orange-size tumors which tend to coalesce and become lobulated. The tumors are yellowish brown or brownish red in color and are rather firm but elastic to the touch The sites of predilection are the face, especially the nose eyelids, lips and ears, and the extremities, particularly the backs of the hands. Occasionally the distribution is more or less general. The mucous membranes are seldom involved. Subjective symptoms are absent. The lesions develop rapidly and after attaining a certain size may persist unchanged for months or years. They rarely ulcerate and, when spontaneous regression occurs, scarring does not result.

Lymphatic Leukemia With Skin Lesions.—The tumors, usually numerous but occasionally solitary commonly appear with the eruption of a number of small papules, and these increase slowly in size and number Erythematous macules and slightly indurated plaques are common. In many cases diffuse though not completely generalized swelling of the skin is associated with discrete cutaneous tumors. Erythrodermic lymphatic leukemia is occasionally primary in the skin before visceral involvement. Extensive ulceration and gangrene may occur as a result of hemorrhage, as in a case of Sarkany and Ransom (BMJ 1 18 1955) see Figs. 977 and 1765

Switzer (J 67: 1511 1916) reported an interesting case of leukemia cutis with mediastinal nodes, but the blood findings remained normal. Universal or diffuse lymphadenosis of the skin due to lymphatic leukemia is a rare disorder and is readily confused with the érythrodermie prémycosique which progresses into mycosis fungoides. Gattwinkel (AfDuS 175: 578 1937) added 1 case to 5 he found in the literature of primary erythrodermic lymphatic leukemia of the skin without visceral involvement. Wise (JCutD 35: 609, 1917) observed such a case; the patient was greatly relieved by x ray therapy Rosenfeld and Straumfjord (AIntM 57: 758, 1936) described a woman 60 years old with pruritic xfoliative dermatitis and nonulcerati nodules. The Negro patient of Hitch and Smith (ADS 36 1 1937) presented the linical picture of pemphigus fol aceus. Bertaccini (DWehr 99 741, 1934) observed a papual eruption on the limbs of a lymphatic case.

An analysis of 259 cases of lymphatic leukemia was made by Beek (Dermatologica 96 350, 1949) Skin tumors were found in half the cases. The ge range was from 55 to 64 years, and 69% of the patients were males. Erythroderma occurred in about 25% herpes zoster in an equal proportion, prurigo-like lesions in slightly fewer bullae in 10% and purpura in 5%. Lesions resembling varicella occurred in from 3 to 4%, and urticaria n an equal number Only about 8% of the patients with tumors showed ulceration of them. The head was involved with tumors in some two thirds of the patients who had tumors, th legs and arms in about a h lf the tru k n 40%, the mucous membranes in about 10%. Leonine facies developed in about 5% Half of the patients with tumors developed herpes zoster the lesions of which were gangrenous in 60% of the nstances in which t occurred. It was usual f r lymphati tumors to develop in the scars of herpes zoster Attention has been alled to this curious rel tionship between herpes zoster and leukemia by Barney (ADS 37: 238 1938) who reviewed the lit rature, and by numerous case reports, such as those of Catlin (BMJ 1 601, 1946) nd Wilkinson (BJD 59: 57, 1947) Generalized herpes zoster and encephalitis complicated the case of Frank (ADS 64 192, 1951)

Myelogenous Leukemia With Skin Lesions.—Lesions include specific tumors (leukemids) erythroderma bullous eruptions and rosacea like eruptions. The appearance of cutaneous manifestations in chronic myeloid leukemia presages the terminal phase.

Nonspecific skin manifestations in myeloid leukemia, as listed by Costello et al. (AD 1 603 1945) are most frequently pruritus, prurigo urticaria, erythema multiforme-like lesions, papulovesicles, subcutaneous nodules, petechiae and hemorrhages. Pruritus is a variable symptom, often associated with specific lesions. Prurigo, when it occurs, affects the extensor aspects f the extremities and consists of numerous minute itchy, brownish, yellow papules which may show vesiculation and crusting (Steinbrink and Stukowski ZtschrKlinMed 101 375, 1925) Urticaria often occurs in leukemia cutis the lesions are more persistent than in ordinary urticaria, may accompany other eruptions, and may follow x-ray therapy

A case of myelosis in the kin and 14 found in the literat re were presented by Hollander et al. (ADS 29: 821, 1934) Some 44 cases w th skin lesions were collected by Nékám (BeoclangD 44: 1236, 1937) An initial predilection for areas exposed to light





Fig. 1750.—Myeloid leukemia. See Fig. 1752. (Ketron and Gay [illegible] 1923.)
Fig. 1751.—Lymphatic leukemia. (Dr. Gustav Riehl.)



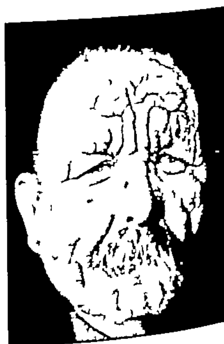


Fig. 1752.—Myeloid leukemia of the skin. (Drs. Ketron and Gay.)
Fig. 1753.—Leukemia cutis. (Dr. E. L. Sweitzer.)

may result in early lesions simulating lupus erythematosus or sarcoid, noted Costello et al. (AD 71: 603, 1955) in their exhaustive review. The nodular infiltration of the skin of the chest was typical in the patient of Goldhamer and Barney (J 107: 1041 1936). When skin lesions make their appearance rapidly the end is near according to Paul and Limarzi (ADS 45: 697 194.)

A fair proportion of the patients remain aleukemic, such as those of Opfer (DWchn 101: 1479, 1935), Zimmerman and Curtis (ADS 33: 684, 1936), Mettier and Purviance (AIntM 60: 458, 1937). Leukopenia in fact characterized the whole or greater part of the course in c was reviewed by Scott (ProcRoySocM 3 : 1420 1939) who found no age or sex preference in these patients, and who pointed out as cardinal symptoms anemia, a hemorrhagic tendency and proclivity to necrotic angina, which are especially notable in the acute cases. Purpura, splenomegaly and ulceration of the leg were the features in the old

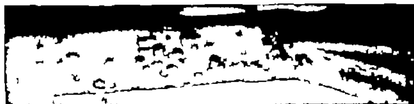


Fig. 1754.—Leukemia reddish brown nodules in skin (Dr John Butler)

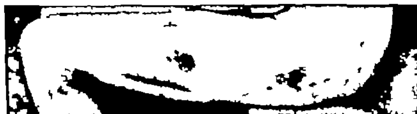


Fig. 1755.—Leukemic lesions with ulceration, thigh. (Dr A. B. Cannon.)



Fig. 1756.—Myelogenous leukemia with gingival hypertrophy and hemorrhage. (Thoma: Oral Pathology Mosby 1954.)

woman reported by Polson (BMJ 461 194) Angina and ulceration of th forearm followed by ulcerative petechiae and bleeding from mucosae were notable in a patient of Herzberg and Schuppener (DWch 122 639 1930) The i fant born t a woman with m eloid leukemia d d not have the disease noted Kucharick (SchweizMWchn 78: 624 1948)

An i fant born with myeloid leukemia was reported by O Connor et al. (AmJDisChild 6? 740 1954) and another a baby girl with specifi skin nodules that progressed by Reims t al. (JPediat 46 416 1955)

Monocytic Leukemia.—First described by Reschad and Schilling (MünchMWchn 60 1981 1913) the Naegeli type a variant of myeloid leukemia with a predominan e of monocytes, was distinguished from the Schilling type which is a leukemic reticuloendotheliosis, by Griffin and Watkins (AmJMedSci 188

761, 1934), according to Montgomery and Watkins (AIntM 60 51 1937) Either may begin primarily in the skin. Monocytic leukemia comprises about 5% of the leukemias, of which some 62% are myeloid and 33% lymphatic (Osgood AIntM 59 931, 1937) Ages ranged from 11 months to 78 years in Osgood s collection of over 130 examples, 67% of which affected males. Swelling of the gums was present in 80% of them and was sometimes the first symptom, and purpura was present in 70% The spleen was enlarged in 84% the lymph nodes in 77%

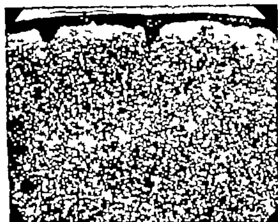


Fig. 1737 —Leukemia cutis (Dr Grover W Wende.)

Mercer (AD&S 31 615 1935) collected some 51 cases of monocytic disease among which his * pat nts exhib ted diffuse e anthems of slight red macules changing to slate blue also firm pale papules a few large nodules and some lesions purpuric in appearance which n section were actually leukemids. Subcutaneous nodules were present in the woman reported b Lo eman (SouthMJ 29 337 1936), who reviewed the literature. Eight cases, * with lcerati were described by Lynch (AD&S 34 ...5, 1936). Montgomery and Watkins (MinnM 1 636 1938) reported 4 cases of the Schilling t pe with exfoliative dermatitis, in which t pe ulcerative gingi it i not common. Th erupt on seemed typical to Freeman and Kolet ky (AD&S 40: 13, 1939) in that it begins maculopapular simulating

secondary syphilis, and evolves from day to day sometimes disappearing in areas. Necrosis of the skin, especially at the folds, and the change from aleukemic to leukemic with a total white count perhaps less than 20,000 are ominous, and the course is sometimes fulminating according to Herbut and Miller (AmJPath 23: 93, 1947) whose cytologic studies of 8 cases were interesting

Lymph node and splenic enlargement are not extreme when present. Pallor weakness, low fever and bone and joint pains are common accompani



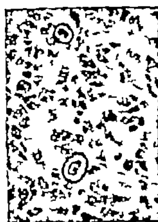


Fig 1758.—Leukemic nodule in skin.
Fig 1759.—Monocytic leukemia, cutaneous lesion; encircled cells show folded ben ppearance typical of monocytes. (Loveman SouthMJ 29: 237 1936.)

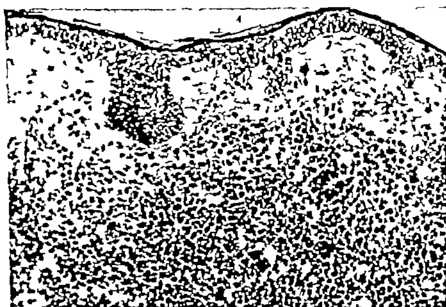


Fig. 1760.—Myeloid leukemia, cutaneous nodule. (Dr Lloyd Ketron.)

ments. In acute monocytic leukemia bleeding swelling of alveolar ridges, mandibular pain and ulcerative and gangrenous gingivitis are seen in perhaps half the cases (Moloney NEngJM 222: 577 1940; Hubler and Netherton ADS 56 70 1947) Purpura and hemorrhagic and bullous lesions seem to be common in the early stages. These features, in fact, are so characteristic that the diagnosis can often be made correctly on clinical grounds (Forkner AInt M 53 1 1934)

A normal infant was born to a woman who died of the disease 8 days post partum reported Williams (AmJObGyn 55 967 1948)

See Nékám (BsocfrançD 44: 1236 1937), 44 cases and review of skin lesions in chronic myeloid leukemia; Emile-Weil (BsocfrançD 44: 1209 1937), skin lesions in leukemias, Gerl and Rosahn (AmJClinPath 13: 516, 1943) leukemic skin lesions without leukemia Hall (ADS 47 792, 1943) case; Aseltine (JOralSurg 2 266, 1944) oral manifestations Freeman (ADS 3 275 1946) acute case, Naegeli type Bluefarb (ADS 57: 319 1947) leukemic infiltrate of spinal ganglion found at autopsy in case with herpes zoster Oliver et al. (ADS 58 511, 1948) man with pustules, crusts bullae, fever and eosinophilia of 56,000, ( ) eosinophilic leukemia. Diaz et al. (abs J 145 64 1951) 7 cases, 5 autopsies.

SKIN LESIONS IN DISCRETE BLASTOMAS OF THE HEMATOPOIETIC SYSTEM

Lymphoma.—The cutaneous tumors of lymphoid hyperplasia are more apt to be large ulcerated and fungating and are somewhat less stable than the tumors accompanying leukemia Single tumors are more common than in association with leukemia but are relatively infrequent. Diffuse infiltration and plaques occur as well as discrete tumors. In the majority of cases lymphoma is of the Hodgkin s disease type See Brill et al. (J 84 668 1925) Gates (ADS 37 1015 1938) Combes and Bluefarb (ADS 44 409 1941) Gall and Mallory (AmJPath 18 381 1942) See Classification (p. 1274)

Giant Follicular Lymphadenopathy (Brill-Symmers) clinically strongly resembles Hodgkin s disease and is usually mistaken for it (Uhlmann Radiol 50 147 1948) It is characterized by local or general enlargement of the lymph nodes often in conjunction with splenomegaly The nodes are relatively soft and the patient s well being is not greatly influenced Histologically the masses suggest lymphoid hyperplasia or chronic lymphadenitis.

In 15 cases studied by Combes and Bluefarb (ADS 44: 409 1941) a variety of clinical dermatologic diagnoses had been made including atopic eczema, exfoliative dermatitis and mycosis fungoides. They called attention to the fact that the process may eventuate in polymorphous cell sarcoma, Hodgkin disease or lymphatic leukemia.

Exfoliative dermatitis wa present in 4 of 19 patient reported by Rubenfeld (J 137: 840 1948), who described the histologic features which clearly distinguish this form of primary disease of the lymphoid system *from* Hodgkin's disease. It is characterized by *numerical and dimensional hyperplasia of the lymph follicles.* These may consist exclusively (1) of small lymphocytes but more commonly 3 types of cells may be distinguished in them: (1) large cells with hypochromatic nuclei, the borders of which are sharply defined and indented (2) smaller cell with richly chromatic nuclei but with similarly indented membranes and (3) cells with still smaller nuclei deeply staining and with poorly defined membranes that resemble large lymphocytes.

The hyperplastic lymph follicles may remain intact throughout the course of the disease or they may rupture and permit escape of their cell components into the substance of the nodes in which case the disease giant follicular lymphadenopathy becomes transformed into polymorphous cell sarcoma. Symmers (APath 26: 1002, 1938) described the transformation. According to Cohen and Bergstrom (AmJClinPath 16: —, 1946), the ability of the disease to alter its morphology appears to be distinctive. Giant follicular lymphadenopathy is to be understood as a pattern of hyperplasia with potentialities for various different at ons, the end phase being unpredictable from the original morphology. On the other hand it may remain unchanged throughout life or it may undergo transformation into lymphosarcoma (Baehr et al. AmJPath 7: 659, 1931) or it may at its lymphoid leukemia or become associated with the histologic changes of Hodgkin's disease or give rise to reticulum cell sarcoma, or finally it may undergo transformation into the polymorphous cell sarcoma of Symmers. See Evans and Doan (AnnIntM 40 451 1954). While small doses of radiation suffice to induce most nodes to disappear Uhlmann thought it advisable to treat the disease as potentially malignant using therapy intended to forestall the evolution of malignancy

Lymphocytoma is the most benign form of lymphoblastomatoid tumor. The lesions are characteristically composed of papulonodules of various dimensions often symmetric in location red brown or violet in color and slow in evolution The surface is smooth. The locations are the face the lobes of the ears, the scrotum rarely the extremities. The health is not affected, the spleen and lymph nodes are not enlarged and the blood picture is normal, excepting perhaps the mild lymphocytosis which may be present Women are more often the victims but there is no predilection as to age

The classification of Epstein (AfDuS 178: 18 1935) was as follows (1) disseminated papular adenoid aggregations (2) isolated lymphadenoid tumors especially of face or ear; (3) circumscribed on scrotum; (4) lymphatic disease of external genitalia (pseudosyphilis papulosa of Lipschütz; see Hooker DWehr 99 1409 1934); and (5) miliary cases like that of Mulzer and Keining (DWehr 55 293 1929)

Cases have been described by Jadassohn (AfDuS 82 297, 1906) Miescher (BeocfrançD 44 1254, 1937) and others. The patient of Bardo and Lang (DWehr 100: 641 1935) was a man 29 years old with a miliary eruption of tiny nodules composed of lymphocytes these authors found only 31 cases in the literature. Gates (ADS 3 : 1013 1943) stated that lymphoma composed of adult lymphocytes is not seen in the skin, and pointed out that the ease with which the cells are as a rule dispersed through the lymph and blood vessels distinguishes the circulating forms from those which tend to be discrete. I should be hesitant to admit the existence of wholly benign adult lymphoma.

The histology is uniform. There is seen the rounded nodule infiltrating intradermally and well demarcated as a rule. The cells are lymphadenoid being mainly small lymphocytes, with characteristically the formation of lymphatic follicles.

Favorable therapeutic results are known to have followed the administration of arsenic. I did a radical excision in 1 patient who has been symptom free for 10 years. X ray therapy is likely to be successful in dosage such as would befit other lymphomas. One might give 300 r weekly at 120 kv with 1 mm. Al, to a total of from 2,000 to 3 000 r



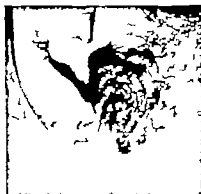


Fig. 1701.—Lymphocytoma. (Hellier BJD 51 360 1939)
Fig. 1702.—Lymphocytoma in woman 44 years old.

See Deep type of discoid lupus erythematosus; also Miescher (BeocfrançD 44 1254, 1937) 3 cases, photograph of Jadassohn 1906 cheek lesion and Kaufmann Wolf 1921 scrotal lesion Carol and Prakken (ActaD-V 20 147 1939) 4 cases Hallam and Vickers (BJD 51 283, 1939) 2 cases; Hellier (BJD 51: 360, 1939) case and classification MacKee (ADS 50 141, 1944), nose, Gawalowski (AmedeD 1945, p 113), 2 forehead cases Lentz and Beerman (ADS 60 ... 1949) follicular papular on man belly; Foerster et al (ADS 60 874, 1949), woman forehead Simpson (BJD 61 ..., 1949) miliary facial Epstein (ADS 60 368, 1949) miliary facial; Barnes and Moffatt (ADS 62 ..., 1950) woman nose, not influenced by P32; Whittle and Lyell (BJD 63 ..., 1951) miliary becoming malignant, Waisman and Olivetti (ADS 64 761, 1951), woman's cheek lesion radioresistant but helped by antibiotics: Loveman and Fliegelman (ADS 63 169 1951) 3 cases, similarity to Spiegler Fendt disease Mopper and Rogin (ADS 63 164, 1951) 2 cases, solitary radiosensitive Wadhurton (BJD 65 217 1953) miliary on woman face Walther (ZtschrHuG 12: 136, 1952), solitary lesion cured by penicillin Alexander and Paslawsky (Dermatologica 109 1, 1954) 4 cases

Spiegler Fendt Disease, described also as "sarcoid because of the formerly heterogeneous connotation of the term, is thought to belong to the hematopoietic blastoma group (Lewis ADS 31: 67 1935) Spiegler (AfDuS 27: 163 1894) and Fendt (ib. 53: 213, 1900) excluded metastatic tumors in the skin and mycosis fungoides from their entity which Kaposi thought formed a clinically fairly characteristic picture of multiple skin tumors. These are firm, elastic and globular are situated in the dermis and beneath it, and are not progressive beyond a certain stage. They sometimes involute spontaneously and are not associated with lymph node or hematologic changes. Arsenic cured or improved the patients. Lewis distinguished the localized, superficial type from the multiple disseminated, collecting 11 examples of the former and 22 of the latter Ages ranged from 8 to 76 years sex predilection was not apparent and the color of the lesions ranged through red, purplish and brown the number from 1 to 200 the consistency from soft to firm and the size from millet seed to walnut, with solitary plaques occasionally noted.

Histologically the lesions are difficult to distinguish from skin nodules of lymphatic leukemia. Their difference from lymphocytoma (q v) is doubtful (Bafverstedt: abs ADS 53: 386 1946)

They are radiosensitive responding to a dose or two of 125 to 200 r (Cipollaro: ADS 53: 166 1946) The case of Sweitzer (ADS 11 481 1925) a disseminated one involuted under x ray therapy relapsed and died of cachexia with numerous shotty papules in the skin and a large nodule in the kidney



Figs. 1763A and 1763B.—Spiegler-Fendt disease sarcoidal lesions, and lymphoblastoma-like histology (Drs. Stuart Way and Harry Alderson.)

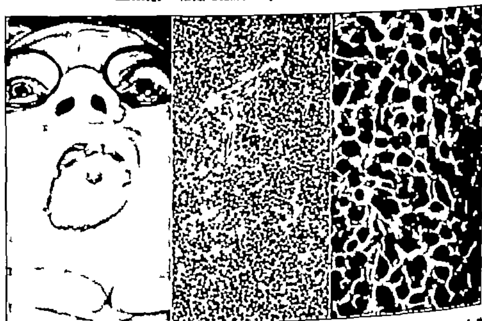


Fig. 1764.—Plasma cell tumor a smooth, round tumor of the hard palate of the size and color of half of a large pea and photomicrographs of this tumor [illegible] (malignant ones lack uniformity of size of cells, be a greater quantity of intercellular material, and have greater and variable quantities of protoplasm) (Hertzler: Surgical Pathology of the Diseases of the Mouth and Jaws, J. B. Lippincott Company.)

See Epstein (ADS 41 [illegible] 1940) reddish brown tumor over man's scapula. Characte[illegible] (ADS 46 483 1942) 41 cases on record; Llambe and Freudenthal (BJD [illegible] 1941) reddish infiltrated plaque on old woman scalp nd forehead; Hestenberg and [illegible] (ADS 61: 675, 1950) young woman's breast Carslaw (BJD 65: 266 1953) woman back

Plasmoma.—The usual tumor of this rare kind is a small lesion of the palate described by Hertzler (Surgical Pathology of the Mouth and Jaws, Lippincott, 19[illegible], p. 2[illegible]) Early as smooth round a d dense but not of bony hardness usually pale bluish in color.

these undergo malignant change, he said, in which case the simple structure is lost the cells stain less uniformly the vessels are more numerous and the vessel walls thinner Extramedullary plasmocytoma was exemplified by a case of Lewis et al. (ADS 63: 474, 1951): an asymptomatic tumor of 3 months duration formed a firm, flesh-colored lesion on the mucosa of a man's nostril. These authors reviewed the subject, reporting that the disease occurs on *mucous membranes, especially of the upper respiratory tract*, sometimes of the conjunctiva. The tumors are firm, bluish red, yellow-gray or dark brown in color diagnosable *only* histologically the microscope revealing a composition almost exclusively of typical plasma cells. They are usually only locally invasive, those of the conjunctiva being regularly benign, but those of the upper air passages sometimes giving rise to widespread metastases. Those which are soft, friable and necrotic or ulcerative tend to be malignant.

Eosinophilic Granulomas.—See p. 1302.

Reticular Sarcoma (Stem Cell Lymphoma) —Robb-Smith (JPathBact 47 457 1938) distinguished reticulosis and reticulosarcoma. Any variant may or may not manifest circulating cells. The sarcomas may show (1) undifferentiation (diffuse or trabecular) (2) histioid differentiation (dictyosyncytical or dictyocytic) (3) hemic cell differentiation (lymphocytic lymphosarcomatous, *myeloblastic, plasmocytic, monocytic or erythroblastic*) (4) differentiation like the cells which line lymph sinuses and, finally (5) mixed types. Robb-Smith (BJD 56 161 1944) simplified his classification of reticulosarcomas into the hemic (lymphosarcoma chloroma plasma cell myeloma) and histioid



Figs. 1788A and 1788B.—"Cellules monstrueuses" *from circulating blood in Sézary's syndrome.* On the right, one is seen undergoing mitosis (Alderson et al. BMJ 1 214, 1953.)

types. In the latter the formation of reticulin is characteristic. Reticulin, collagen and elastica together comprise the 3 types of fibers in the dermis recognition of reticulin histologically was clarified by Robb-Smith (BMBull 3 172 1945) The many variations *of cell type depend on the potentialities for* differentiation of the reticular cells. The diagnostic requirement for blood *and marrow studies is apparent, and for consultation with a competent hema*tologist. The peripheral blood smears were not diagnostic, while the cutaneous imprint smears were in 2 cases of Feldaker et al. (ADS 70 583 1954)

Cases representative of leukemic and aleukemic types were discussed by Weidman (abs YBD 1937 p 326) Leukemia is much more common in the hemic varieties. Nodular infiltrated and indurated lesions of the axillae and groins were observed in one woman, the cells resembling those of primitive mesenchymal syncytial reticulum of lymph sinuses. Rampantly progressive soft, fungating radioresistant sarcomas of this kind, without leukemia, are occasionally seen. The 36-year-old male reported by Wayson and Weidman (ADS 34 755 1936) exhibited a rapid clinical course without leukemia and with skin changes like those *of premycotic and later tumorous mycosis* fungoides. The eyelid is not an exceptional site of origination (Tooke: Brit JOphth 23 444, 1939; *Stansbury AOphth 40 518 1948*) nor is the face (Director and Kern ADS 62 69 1950)

Reticular sarcoma has been known to take the form of pruritus which becomes severe with erythematous plaques on the trunk and limbs becoming generalized. In a case of this sort Sézary and Bouvrain (BsocfrançD 45 254, 1938) found unusual giant cells, cellules monstreuses, in the blood but not in the bone marrow. Such cells are generally 12 to 14 μ in diameter, the large nucleus being surrounded by a thin band of cytoplasm. They have numbered from 2 to over 50% of the white cell total. The patient of Wilson and Fielding (BMJ 1 1087 1953), an old man with exfoliative dermatitis, had a platelet count of some 800 000 while the white cells numbered from 10 000 to 80,000. The distinctive clinical features of such cases are edema of the face, curious cells in the peripheral blood, absence of mucosal lesions, and nonspecific changes in the lymph nodes. Two cases of Sézary's syndrome and a review of 5 others were presented by Alderson et al. (BMJ 1 256 1955)

See Ehrlich and Gerber (AmJCanc 24 1 1935) types of lymphosarcoma; Fraser and Schwartz (ADS 33 1, 1936), axillary and groin lesions in a man; Mayer and Wolfram (AfDuS 181 327 1940) first in arm, maculopapular eruption became generalized and ulcerative; Bingham and Quarrier (ADS 41 722, 1940) rapid fatality; Sugarbaker and Craver (J 115, 17, 112, 1940), 184 cases of reticulum cell sarcoma, Hodgkin omitted; Canal (aba J 149 780, 1952) visceral, dermatologic, and young individual forms of malignant reticulosis with intermittent fever, hemorrhagic syndrome, and final cachexia with edema of lower extremities; Steppert and Wolfram (AfDuS 193: 646, 1952) 4 cases also 1 fibrosarcoma and 1 lymphosarcoma primary in skin.

Hodgkin's Disease may arise in the reticulo-endothelial tissues of the skin, and it may also and more commonly give rise to secondary skin lesions, particularly papules and nodules clinically indistinguishable from those of leukemia cutis. Skin changes occur in roughly a third of the cases; in from 5 to 12% the skin changes come first (Cole J 69 341 1917). The commonest manifestation is pruritus, with or without signs of the general disease; the itching tends to become exacerbated with involvement of fresh nodes. A prurigo-like exanthem on the extensor surfaces, or generally disseminated, may come and go for months. Urticaria is common, but exfoliative erythroderma is rare. Pigmentation is usual and may be spotty or diffuse, sometimes Addisonian, but it leaves the mucosae free. Alopecia, dryness, atrophy and hyperkeratosis of the skin are seen. Cutaneous symptoms may result from icterus and hypoproteinemia when they occur.

Primary tumors may arise in the skin (Senear and Caro ADS 114 1937). The first lesion may be a solitary skin tumor which ulcerates, as in cases reported by Pessin and Pohle (AmJCanc 34 220 1938) and Evans (BMJ 1 13, 1954). While lymph node hypertrophy is the invariable manifestation of Hodgkin's disease, the cardinal diagnostic symptoms of Colrat, splenic and lymph node hypertrophy, fever, pruritus, progressive anemia and increasing polymorphonuclear leukocytosis are not frequently all present (Cleveland CanadMAJ 56 614, 1947).

Some 30 to 40% of cases show skin symptoms, including pruritus, nodules, rarely exfoliative dermatitis and herpes zoster due to ganglion involvement, but mucosae remain free and tonsils are not involved as they are in other lymphoblastomas, reported Goldman (J 114 1611 1940) in a review of 1? cases. The ichthyosiform change sometimes seen (Ronchese: ADS 47 77, 1943) may be due to liver damage and resultant malmetabolism of vitamin A (Glazebrook and Tomaszewski ADS 50 85 1944). Desjardins (J 103 10?, 1934) called attention to the frequency with which the first nodes affected are those draining a site of chronic infection. Warthin (AnnSurg 93 153 1931) demonstrated the transitional interconnection of Hodgkin's disease with other forms of hematopoietic neoplasia, including mycosis fungoides, with or without leukemia.

The diagnostic technic and interpretation of lymph node imprints, following Schleicher, was discussed by Sweitzer and Winer (ADS 51: 2?? 1945). The histologic features of mycosis fungoides are pyknosis, karyorrhexis and cellular detritus and are in Hodgkin's disease in which distinctive Sternberg-Reed cells appear to be proliferations of reticulum cells and polymorphism of the infiltrate is conspicuous, whereas the infiltrate of the leukemias is monomorphous.

The multinucleated Sternberg-Reed cells, identified as diagnostically significant by Reed (JHHospRpts 10: 133 1902) were first noted by Greenfield (TrPathSocLond 29: 272, 1878) They are probably derived by progressive alteration from free reticulum cells (Hoffman and Rottino: Blood 5: 4 1950) Diagnostic in a suggestive way is the observation of deWinter (BMJ * 604 1938) that regions of bony metastasis become painful when alcohol is ingested.

GORDON TEST—Intracerebral inoculation into rabbits of sterile suspended lymph node material from Hodgkin's disease produces an encephalitic response which Gordon (BMJ 1: 641, 1933) thought specific. The Gordon test is dubious, according to MacNaught (J 111: 1280, 1938) who ascribed the reaction to the presence of eosinophils rather than a virus. The test, nevertheless, is of value if interpreted in conjunction with histologic study according to Steiner (APath 31 1 1941)



Fig. 1766.—Lymphoblastoma, with large ulcerative lesions (Dr E. J Angle.)

Fig. 1767 —Leukemic nodules in skin of ear

Fig. 1768 —Exfoliative dermatitis of legs in Hodgkin disease. (Derasek J 126 1023 1944)

Fig. 1769 —Hodgkin' disease cutaneous infiltration (Dr Henry Michelson.)

PROGNOSIS AND TREATMENT —Of 472 cases of lymphoblastoma reviewed by Minot and Isaacs (J 86 1185 1265 1926) 68% of the patients were males. The peak incidence of onset was in the group 20-24 years of age and was due to Hodgkin's disease there was a secondary peak in the group 35-39 years of

age, due to diseases other than Hodgkin's. The expectancy seemed to be influenced but little by x ray therapy The use of surgery early followed by radiation given afterward as needed, seemed to prolong life. The average survival time after diagnosis was 2.76 years, but 10% of the patients survived for 10 years or longer Radiation therapy relieved some of the symptoms without prolonging survival time Minot and Isaacs believed.



Fig. 1770.—Hodgkin's disease, primary in skin. (Evans BMJ 1 136, 1944)





Fig. 1771—Hodgkin disease: ulcerative cutaneous tumor of the anterior chest w . (Wiener Skin Manifestations of Internal Disorders, Mosby 1947)

Fig 1772—Hodgkin disease with specific cutaneous lesions. See Fig 1771. (Bernard J 126 1025, 1944.)

If the disease can be recognized in its early skin primary stage it is probably worth while to perform a wide surgical excision (Osborne ADS 51 436 1945 Lever ADS 61 1070 1950) This is likewise probably true when it begins in lymph nodes, provided the lesion is localized (Bernard and Ostpor skl abs J 142 1030 1950) one would follow up with radiotherapy See discussion of surgical attack in Jackson and Parker (Hodgkin's Disease and Allied Disorders, Oxford U Press, 1947)

The complications of lymphoblastoma, including Hodgkin's disease were studied by Desjardins et al. (AmJRoentg 36: 169 1936) Fever pruritus, skin infiltration, orbital infiltration, erosion of the sternum, injury to recurrent laryngeal nerve, tracheal obstruction, edema, osseous lesions, spinal cord compression, nerve infiltrations, brain lesions—all are possible and several are likely In x ray treatment they advised the avoidance of maximum doses in the obtaining of good symptomatic relief. It is usual for the lesions to respond well at first and become progressively less responsive to radiation. Prognosis is more favorable when the involved nodes are accessible and systemic symptoms are minimal, and surgical attack in such cases is justified, according to Slaughter and Craver (AmJRoentg 47: 596, 1942) whose review of Memorial Hospital experience showed survival time from the start of therapy to be 5 years in 18% and 10 years in 3.4% the average survival time of those who died was 3 years. Full doses of x ray therapy were advised by Marner and Stenstrom (Radiol 43 355, 1947) who gave 1,000 to ,000 in 3 weeks, treating the most distressing nodes first; the 5-year survival rate was 21%.

Of 113 patients treated at the Ontario Institute of Radiology 19 4-194., 51% survived 5 years and 35% survived 10 years, reported Peters (AmJRoentg 63: 299, 1950) Progress and ultimate survival were importantly concerned with the extent of involvement and the presence of constitutional symptoms at the time therapy was begun. At the





Fig. 1773.—Hodgkin's disease in the skin. (Dr D. B. H. Cleveland.)
Fig. 1774.—The trunk of patient shown in Fig. 1773. (Dr S. R. Barnack.)

Radium Center Copenhagen, during 1930-1945 173 patients were treated with daily doses of from 100 to 200 , to totals of from 800 to 1,500 r, depending on the effect, region and tolerance reported Videbaek (ActaMScand 136 203, 1950) The average duration of illness was about 3.5 years, children doing best and old people worst.

Palliation with sulfonamide by mouth, inducing diminution of the white blood cell count, was noted by Urbach (ADS 41 181 1940) Irradiation, TEM and NH, are the most effective therapeutic measures vailable (Meyer J 154: 114, 1954) See Chemotherapy of malignancy (p. 1300)

Hodgkin's Disease.—See Greenbaum and Cornell (ADS 33: 549, 1936) primary in scalp; Potter (APath 19 138, 1935), histologic diagnosis; Wrong (ADS 33 [illegible], 1936), primary in scalp Durand et al (PresseM 44 1723, 1936) chest ulcer primary in girl, Ha (EdinMJ 40 408, 1939), pruritus, erythroderma, intracranial metastasis Kravitz (AOphth 21 [illegible], 1939) cystic primary supraorbital in old woman; Uhlenbeth and Wurm (abs J 113 2482, 1939) review of etiology ( ) infection; van Buchem and Batman (BJD 52 304 1940), nodules in face Wise and Poston (J 115 1076, 1940) coexisting brucellosis, Richter (ADerm 181 1, 1940), case with papula urticaria, review of skin manifestations Kierland and Montgomery (PMC 16 124, 1941) rare cutaneous ulcers; Tappeiner (ADerm 181 126, 1941) skin involvement in 13 cases, classification; Reimann et al. (AIntM 70 434 1942), subcutaneous nodules simulating panniculitis; Dunnan and Johnston (PaMJ 46 1183, 1943) 37 cases, 6 with skin lesions, all nonspecific; Anderson (BMJ 1 721, 1944) typical cases like those of Scott and Robb-Smith (Lancet : 194 1939) with fever wasting, general lymphadenopathy, leukopenia, purpura, jaundice, tender purplish lumps in forehead, cheeks, neck, upper chest and back and proximal parts of extremities, with rapid fatality, Barnack (J 126 1015, 1944) ulcerative nodule of leg with terminal miliary metastases; Goldman and Victor (NYSJM 45 1313, 1945) skin involved in 39% of 313 cases, 11 pregnancies with no evidence of trans-

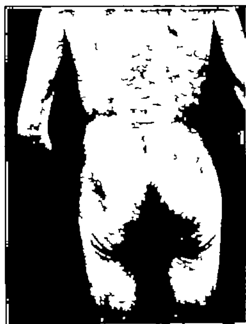




Fig. 1 76.—Hodgkin's disease of the skin, showing dryness, pigmentation, and scaling (Dr A. Benson Cannon.)

Fig. 17 6.—Hodgkin disease, showing subepidermal infiltrate of large and small lymphocytes and an occasional multinucleated Sternberg Reed cell. (Dr H. E. Michelson.)

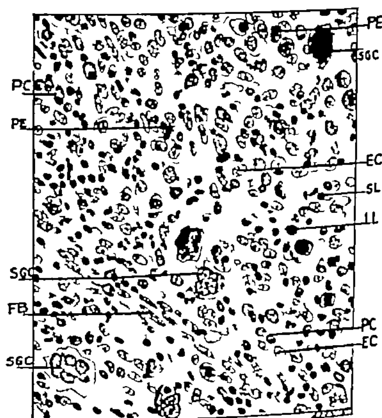


Fig. 1 77.—Hodgkin disease polymorphous granulation tissue characterized by presence of Sternberg giant cell (SGC) EC epithelioid cell FB fibroblasts PE eosinophils PC plasma cells SL small lymphocyte LL large lymphocyte (Michelson Histopathology of Skin Diseases Mosby 1931.)

mission to fetus, Charache (NYSJM 46 507 1946), 11 cases in children; Hoster et al. (OhioMJ 43 721 1947) etiology (?) infectious, tissue-culture in estimations; Van Der Meiren (BJD 60 131 1948) 3 skin primary cases Hoster et al. (CancRes 9: 473, 1949) favorable effect of virus hepatitis coincidental in 3 cases Cattinella (AD&S 60 351, 1949) on set on thigh with vesicles becoming shallow ulcer; Sabyoun and Eisenberg (AmJRoentg 61: 369 1949) cytologic prognosis; Edit (J 139: 380 1949) incidence of 0.5 to 2.5 per 100,000 seems increasing; Grand (CancRes 9: 183, 1949) viral ( ) cytoplasmic inclusions in tissue cultures; Edit (J 144 764, 1950) (?) virus etiology Eichel (ActaRadiol 33 427 1950) pregnancy 65 instances in 57 women, parturition and puerperium ran normal course, 1 case on record of apparent transmission to infant, Pollock (AD&S 62 759, 1950) scalp primary, Fairburn and Bettley (BJD 62 504, 1950) skin primary in man with topic dermatitis and ichthyosis; Bostick and Hanna (CancRes 11: 505, 1951) serial passage of extracts from diseased lymph nodes in chick embryos Newman and Pushkin (J 146 335, 1951), fulminant case, fever jaundice, purpura, onset 2 weeks after tattoo Gledhill and Shilleto (BMJ 1 1336, 1952) amyloidosis] Hodgkin disease Isch-Wall (Sang 23: 650, 1952) colchicine treatment ; Hines and Frelick (AmJRoentg 70 247 1953) 19 cases, with 5-year survival in 9



Fig. 1778.—Mycosis fungoides early stage of erythematous eruption. (Dr Grover W Wende)

Dervis and Decker (SemMed 30 197 1954) prognostic statistics in 182 cases; Johnston (BMJ 1 916, 1954), spontaneous remissions in natural history of the disease Foreign Letter Brazil (J 154 1105, 1954) histoplasmosis and Hodgkin disease, 7 coincidence Funkhouser et al. (J 156 472, 1954), prognosis unreliable but influenced by therapy; Portmann et al. (AmJRoentg 72 772, 1954) gastrointestinal manifestations may be initial ones, primary lesions of the stomach and bow l; Hearn (BMJ 2 832, 1954) itching relieved by injections of Adrenalin Healy et al. (Radiol 64 51 1955) 216 cases, review 1 000,000 of therapy evaluated f orably Spaddon (BMJ 1 763 1955) equired ichthyosis l 4 cases of Hodgkin disease and reticulosarcoma.

Mycosis Fungoides is the clinical syndrome first described by Alibert (Maladies de la Peau, 1814) in which hematopoietic neoplasia with conspicuous cutaneous manifestations evolves gradually as a chronic affection, its course being usually marked by 4 fairly definite stages (1) the stage of dermatitis (2) the stage of infiltration (3) the stage of tumor formation; and (4) the stage of ulceration. In the first stage the manifestations may assume

variable forms particularly that of parapsoriasis en plaque (q v) sometimes that of poikiloderma atrophicans vasculare (q v) In the presence of a chronic ambiguous, pruritic dermatitis, rebellious to treatment and manifested by circumscribed plaques resembling erythroderma, psoriasis, urticaria, or lichenified prurigo it is necessary to bear in mind the possibility of mycosis *fungoides. After a more or less prolonged period of variable and largely* macular manifestations some rounded or reniform lesions become infiltrated, and textural changes persistent. The period of tumor formation gradually follows that of infiltration. The growths are round or oval, pea to orange size





Fig. 1779 —Mycosis fungoides, involving the tongue. (Dr George M. Mackee.)
Fig. 1780 —Mycosis fungoides, early tumors. (Dr H. M. Robinson.)



Fig 1781 —Mycosis fungoides. (Dr J Lamar Calloway)

or larger whitish, pinkish or purplish solid smooth or crusted *tumors*, rarely being pedunculated. They may disappear spontaneously and new ones may spring up on diseased or apparently normal areas at any time *Ulceration* generally occurs first at the apices of the larger growths, and usually only a portion of the tumor becomes necrotic. The lesion is then a tomato-like ulcerating mass, the gangrenous surface of which is covered with sanguineous exudate

Tumors appear in two forms (1) the rare mycosis fungoides à tumeurs d emblée in which they appear suddenly and of which Gates (ADS 37 1025,





Fig 1782.—Mycosis fungoides.
Fig. 1783—Mycosis fungoides, a large scalp tumor (Dr J Lamar Calloway)





Fig. 1784—Mycosis fungoides, showing multiple large tumors on upper extremity (Dr Clyde L. Cummer)
Fig. 1785.—Mycosis fungoides, tumor of hypothenar region. (Dr J Lamar Calloway)

1938) found only 4 cases in the literature and (2) more common, cutaneous tumors developing on the basis of dermatitis. The premycotic lesions, localized or diffuse, and described as simulating eczema, urticaria, lichen planus or even pemphigus, are in no way distinct from the early lesions of leukemia or other lymphomas. These premycotic lesions precede the formation of tumors over shortening intervals for months or years. A common premycotic lesion is desquamative dermatitis with pruritus, l'homme rouge Lymph node involvement may be present as it usually is in exfoliative dermatitis, but is not of itself a characteristic feature.



Fig. 1766—Mycosis fungoides, late tumor stage. (Dr E. L. Stewart)

The preliminary stage may be brief or even lacking the growths developing on apparently normal skin, but usually it is present and may last for months or even years before infiltration becomes apparent. The patches are usually circinate in outline and may be either dry or moist. A case of Senear (JCutD 33 351 1915) began on the right foot as a pea-size, subcutaneous nodule with associated pruritus, one of Biddle (Phys& Surg January 1900) as a generalized variegated psoriasiform eruption, and one of Ormsby (Med 9 904, 1903) as an efflorescence which could not be differentiated from parapsoriasis. The color of the lesions ranges from pinkish or reddish to a purplish or brownish hue Itching may be absent but is generally present Early manifestations are as capricious in their course as they are various in appearance The eruption may almost disappear spontaneously at any time only to recur at the same site or in some other locality in a few weeks.

The second stage is the lichenoid period of Bazin during which circumscribed areas of infiltration appear The lesions range from pea to palm size and may be commingled with the erythematous and eczematous plaques of the first stage. They too are oval or circinate in outline, but as a result of involution and of coalescence crescentic and gyrate lesions may be formed. Ulceration sometimes occurs at this stage

The period of tumor formation gradually follows that of infiltration. The growths are round or oval, pea to orange size or larger whitish, pinkish or purplish solid, smooth or crusted tumors rarely pedunculated. Their number ranges from a few or several to a score or more. No region is exempt. The course of the tumors varies. They occasionally disappear spontaneously and new ones may spring up on diseased or apparently normal areas at any time. They are seldom tender or painful. They may be itchy but pruritus is not a prominent feature of this stage of the disease.

Ulceration generally occurs first at the apices of large growths, and usually only a portion of the tumor is destroyed. The resulting lesion is a mushroomlike ulcerating mass.

Oliver (ADS 10: 183 1934) reported 3 cases of the tumor d'emblée type, in none of which had occurred signs of a premycotic stage. Th case of Semon (BJD 38: 185 1926) also was of this type; it occurred in a healthy looking man of 64 whose tumors disappeared like magic after a single erythema dose of x ray

A hyperkeratotic and verrucous involvement, especially of volar skin, resembling tuberculosis verrucosa cutis, accompanied by typical lesions elsewhere, first described by Hallopeau and Bureau in 1896, was seen in 2 cases by Jeanselme and Bernier (AnndeD 7: 65, 1926) Millan and Périn (BsocfrancD 30 894 1923) reported a similar case. S ch a case was observed by Asel et al. (ADS 63 633, 1951) who, finding the disease unresponsive to an antimonyl used x ray therapy which was promptly effective.

A mother was the victim reported by Cameron (ADS 27: 233, 1933) and her daughter died of mycosis fungoides (Wile and Knerlert ADS 39: 039 1938) Lane and Greenwood (ADS 27: 643 1933) recorded case in which mycosis fungoides and Kaposi's sarcoma occurred in the same person. In the patient of Ketron and Goodman (ADS 24 759 1931) were multiple lesions of the skin, apparently of epithelial origin, which clinically resembled mycosis fungoides.

A review of 432 cases collected by Jordan and Arecshewa (DZtsch 74: 120 1936) showed peak incidence in the group 35-55 years f age. Internal metastases were rare. Death was usually long delayed and due to cachexia and intercurrent disease sometimes hastened by x ray therapy In the terminal stages th proportion f polymorphonuclear leukocytes increased, and that of lymphocytes diminished, in the peripheral blood. Of 49 cases seen in Berlin from 1920 to 1937 34 were typical, 2 were fulminating, 7 erythrodermic, 3 d emblée, and 3 individual and curious (Berggreen: AfDuS 178: 501, 1939) Lymph nodes w re affected in 6, the mucosae in 3, and the liver pleura and lungs in 3 each. Eosinophilia sometimes ranged from 20 to 60% without leukemia. The duration ranged from 7 months to 34 years, the age at onset from 22 to 75 Cachexia and intercurrent infections were the causes of death.

Pathology —In the premycotic stage Galloway and Macleod (BJD 12: 153 188 1900) found connective tissue cell proliferation around the blood vessels of the subpapillary and papillary layers, the hair follicles, arrectores pili, sebaceous glands, coil ducts and occasionally around the coil glands as well as in foci independent of these structures situated among the connective tissue bundles. These cells were of distinct types (1) large oval fusiform or rounded connective tissue cells containing large nuclei the chromatin network and nuclear membranes of which were darkly stained while the nucleoplasm was more densely stained than the cellular protoplasm unless the cells were undergoing mitosis, when the figures appeared deeply colored (2) small round cells of slightly variable shape somewhat larger than leukocytes, with nuclei similar to though proportionately smaller than, those of the large cells, and (3) mast cells of various sizes, along with a few plasma cells and occasional giant cells. In the stage of tumor formation and ulceration proliferation was increased, and the cells showed a marked tendency to undergo necrosis. Both collagen and elastin became basophilic in reaction and tended to disintegrate

In mycosis fungoides, that clinical condition which i ften cl ssed with lymphoma the cellular infiltrate is variable and may resemble that of Hodgkin's disease of lymphoma

or even of *leukemia* (Gates, 1938) "Pyknosis and karyorrhexis are more common than in other tumors, and there is said to be a characteristic clumping of tumor cell There is, however no more uniformity of opinion on the pathologic than on the clinical aspects of mycosis fungoides (Montgomery: ADS 27 253, 1933) A typical mycosis cell measuring from 8 to 12 microns in diameter and having an eccentric nucleus was described by Strobel and Hazen (JCutD 29 147 1911)

The changes may be interpreted as those of reticulum cell dysplasia (Winer ADS 56: 480 1947) The tumors are similar to those in chronic aleukemic or leukemic monocytic leukemia, and variations are due to the diverse potentialities of reticulum cell differentiation, Winer believed.

The patient of Wile and Stiles (J 104 532, 1935) was one of many in whom clinical mutation of lymphoblastoma, mycosis fungoides and Hodgkin s disease has occurred. The interpretation by Fraser (ADS 11: 425 1925) of mycosis fungoides as a variety of lymphosarcoma was an early one; he showed in a fungoid case typical perinephritic infiltration such as occurs in leukemia.

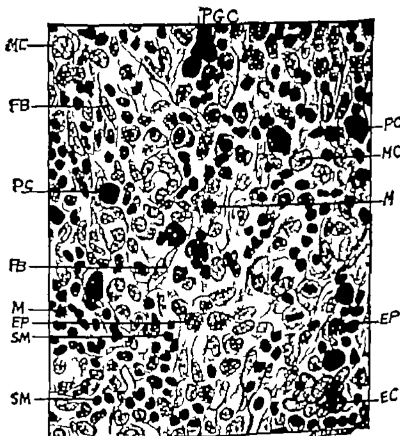


Fig 1787 —Mycosis fungoides *MC* so-called mycosis cells (lymphoblasts); *PGC* ... *M* rechalko giant plasma cell *FB*, fibroblasts; *PC*, plasma cells *EC* epithelioid cells ... *M* mitotic figures *EP* polymorphonuclear ... t giant cell formation *SM* small mononuclear cells ... eosinophil cell Polymorphous character of infiltrate is show (McCarthy Histopathology of Skin Diseases, Mosby 1931.)

An emulsion of a skin tumor obtained from a woman who was observed for 9 years u t l she died and who had nodules in kidney was i jected by Stratton (ADS 48 57 1943) into m ce producing a nodular leukemoid infiltration in the liver spleen and k dneys. Stratton (JID 11: 30 1949) pursued such investigations, obtaining growths in the eye and heart of inoculated chick embryos.

DIAGNOSIS —Incipient mycosis fungoides is to be distinguished from the commoner diseases it mimics. The color contour and erratic course of the *lesions and their resistance to treatment* should serve to arouse suspicion. The occurrence of infiltrative changes suggests the serious disorder *It is only in* this stage of the disease that it can be positively differentiated on histologic grounds from psoriasis and parapsoriasis and identified as lymphosarcoma (Fraser JCutD 35 793 1917 ADS 11 425 1925) Cannon (JMAAlabama

1 454 1932) emphasized the importance and necessity of early and thorough laboratory study One can, as he stated, "say with a degree of certainty that a case was just as truly one of mycosis fungoides when first seen with the eczematoid areas as it was a few years later when the final diagnosis was established The difficulties of assigning particular cases to explicit categories of lymphosarcoma were exemplified by 2 patients of Goeckerman and Montgomery (ADS 24 383 1931)

Bone marrow changes were studied by Lapière and deWeerdt (Sang 13: 393 1939), who found reticulo-endothelial reactions of various intensity to be the most typical medullary modification. The histioid lymphocytes accounted for the greatest part of the observed abnormalities, but characteristic mycosis fungoides cells were not fou d in the bone marrow They pointed out the following abnormalities (1) a polymorphous histioid reaction, rarely absent but remaining discrete except in advanced cases; ( ) an inconstant eosinophilia, with o without eosinophilia of the peripheral blood; (3) inhibition of the transformation of metamyelocytes into neutrophils; and (4) disturba ces in the maturation of the erythroblasts.

Needle aspiration of a skin lesion, smeared and stained, som times yields demonstrable mycosis fungoides cells (Swille et al. ADS 6 : 403, 1953) These cells are apparently immature and atypical histiocytes, with clear cytoplasm and large irregularly shaped, deeply staining nuclei (Lever : Histopathology of the Skin, Lippincott, 1949 p. 424)

The study of 10 patients who came to necropsy by Cawley et al. (ADS 64: 255 1951), was informative. Staging of the disease clinically appeared highly artificial. No typical blood picture could be discerned. Bone marrow ch nges were specific i oal 5 of the 10, but organs other than the skin were involved in 8 of them. Spont eous invol tion of tumors was observed in 2 patients. One had remarkable, bullous lesions. The average length of life after diagnosis was 5.3 years. The final histologic diagnoses were various forms of lymphoblastoma, among which "mycosis fungoides appeared to be a clinical but not a pathologic entity

Symmers (ADS 25: 1, 1932) protested against continuing the use of the diagnosis "mycosis fungoides. Quite possibly it will eventually be discarded, although it still has clinical usefulness.

Treatment —In a few instances recovery is said to have ensued but death may be anticipated in from 1 or 2 to 10 years. Gates (1938) found that the median duration of premycotic lesions in 15 cases was 4½ years, and that duration of life after the development of cutaneous tumors tended to be longer in cases of mycosis fungoides than in cases of lymphoma. X ray therapy has long been known to be effective Relatively small doses of any 150 r at 120 kv with 1 mm. Al filtration, given weekly for several treatments, suffice to resolve most of the skin lesions until, in late stages, they eventually become radioresistant. The ultimate benefits of x ray therapy were considered slight by Herte (ZtschrHuG 13 174 1952) who evaluated 153 cases statistically Advanced cases treated with large doses of P^{32} by Larsson (ActaRadiol 37: 577 1952) showed high uptake of the radioactive substance in the lesions and underwent temporary remission Thorium-X in isopropyl alcohol, 2,000 esu/Gm., may relieve itching if applied weekly for 6 doses, stated Green (BJD 59 384, 1947)

The remarkable effects of high-energy electrons have been discovered only recently Equipment used by Evans et al. (AmJRoentg 69 623 1953) a Massachusetts Institute of Technology electrostatic accelerator of the Van de Graaff type will not soon be in the office of every practicing dermatologist, but it has been known to evoke noteworthy improvement in cases of this disease (Hare et al.: ADS 68 635 1953)

Nitrogen mustard (q.v) was no help to the patient of Friedman (JID 10 227 1948) Used by Newman (ADS 60 215 1949) there was some improvement of the lesions, but the reaction to medication was considerable observations which were confirmed by Graul and Helte (DWchn 122 1071; 1095 1950)

Of the various internal remedies which have been used with laim f benefit, arse ous acid and sodium arsenate must be mentioned, and arsphenamine (Klingsbury: JCutD 31 417 1913; Pechet ADS 1: 711 1920) Wise (YBD 1940 p. 369) thought that the combination of "% sodium arsenat and x ra therapy might keep a patient alive for from 10 to "0 years. Opposition to the use of arsenic was voiced b Levin and Behrman (ADS

51: 307 1945) Coley's serum has been tried, typhoid vaccine helped a patient of Fordyce (JCutD 37: 263 1919) malaria therapy (Fields: UOutRev 40: 262, 1936) and various forms of fever therapy (Klauder: J 106: 201, 1936) have been recommended and intercurrent erysipelas improved the patient of MacCormac (BJD 45: 237 1922) Chaulmoogra oil was palliative reported Lomholt (Hospitalstid 78: 79 1935) and was said to have stopped pruritus when x ray therapy did not, by Wilson (SouthMJ 31: 675, 1938) O'Leary (ADS 54 685, 1946) thought it worth while to try chaulmoogra oil, from 2 to 6 cc. daily for 30 doses, fever therapy and the maintenance of a deep sun tan with ultraviolet light treatments in the premycotic stage. PABA proved disappointing in a case of Mitchell (ADS 60: 885; 900 1949) Strauss (ADS 35 544, 1937) said he had seen improvement following the use of sodium silicate, Loithlen's idea, also used (abroad) to allay pruritus.

The effectiveness of antimonyl preparations (Garb: JID 10: 43, 1948) was reviewed and reaffirmed by Garb (ADS 6 : 463 1953) who found antimony potassium tartrate, Fuadin and Stibanose sometimes helpful. Cases have been known to clear completely and remain in remission for as long as 4 years. Injections should be given, he believed, at least 3 times a week and continued for 6 months after lesions have regressed. Dramamine helps to control nausea if the medicines cause it.

Testosterone made the patient of Garb and Wise (ADS 43: 359 1943) feel better and the studies of Garb (ADS 49 315 1944) indicated that adrenal insufficiency appertains. There is no doubt that cortisone can contribute to palliation.

Quinacrine yielded apparent improvement in 3 cases of Whittle and Moffatt (BJD 66 324, 361, 1954) 1 of which remained in remission for 7 years.

Locally soothing applications such as calamine lotion and the like are indicated. In the ulcerative stage a mildly antiseptic bath followed by a bland dusting powder may be prescribed Surgical measures are usually contra indicated, for the lesions tend to recur promptly following extirpation, but in selected cases such procedures may be justifiable. Antibiotics topically and internally assist in the control of secondary infection. Blood transfusions, high protein diet, nutritional adjunctives and sedation are to be prescribed as indicated.

The avoidance of certain therapeutic errors is worth mentioning greases promote furunculosis and abscesses and do no good roentgen therapy to excess causes serious asthenia arsenic is a poison as well as a tonic.

MYCOSIS FUNGOIDES.—Wise and Rosen (JCutD 34 95, 1916), case initially indistinguishable from parapsoriasis en plaque Ormsby and Finnerud (ADS 27, 431, 1933), case [illegible] autopsy mycosis fungoides is an entity Zurhelle (DZtschr [illegible] 65, 1934) guinea pig inoculations negative Portnoy (Lancet 2 1016, 1937) 2 cases, 1 radiosensitive, 1 violently malignant Nékám et al (BsocfrancD 44 1279 1937) important review Pautrier et al (BsocfrancD 44 1323 1937) A tumeur d emblée, review and bibliography, Cailliau (AnndeD [illegible] 1940) etiology (?) [illegible] cellular polymorphism, histogenesis Niethammer (AfDuS 179 484, 1940) pulmonary infiltration [illegible] fections, benefit with sulfonamides Werth (AfDuS 181 [illegible] 1940) [illegible] Herman (APath 29 530 1940) mycosis fungoides as leukemic reticulo-endotheliosis Pautrier (Dermatologica 57 [illegible]) (KlinWchr 21 561, 1942) (?) microorganism found in endothelial cells Pautrier (Dermatologica 87 190, 1943) man with soft, reddish-brown tumors which ulcerated, not classifiable Sigel (ADS 52 18 1945) 3 Negro cases; Beerman and Thomas (JID 7 271, 1946), [illegible] case evolving from congenital ichthyosiform erythroderma Post and Lincoln (JID 10 [illegible] 1948) 2 unusual psoriasiform cases autopsied Wirthem and Smith (ADS 57 [illegible] 1948) argue for infective origin, Graefin (Dermatologica 96 337 1948) survey of 1946-1947 literature, Musso (Oncologia 2 149 1949) urethan in 4 cases, helped 2 [illegible]; Tilley and Smith (JID 14 387 1950) bone marrow [illegible] in 6 cases nonspecific Lewis (ADS [illegible] 344 1950) radioresistant case helped by antimony Braunschied (DWchr 121 [illegible]) man with oropharyngeal but no skin lesions, autopsy Herzberg and Ueberschär (DWchr 121 316 337, 1951), 5 cases, 4 at pmes, interpreted [illegible] neoplasia of variable malignancy; McGovern (AustralJD 1 153 1952) mycosis fungoides a hyperplasia of cutaneous reticulum cells which may terminate in Hodgkin's disease, sarcoma or leukemia, according to differentiation.

Etiology and Diagnosis of the Lymphoblastomas.—The cause is unknown The history and course in some cases suggest an acute infection. Local proliferation occurs in the tumors as the presence of mitosis attests. In leukemia the infiltration of the skin and the subcutaneous tissue stops with a sharp line just beneath the papillary layer Special stains such as polychrome methylene blue methyl green, pyronine and a combination of Much Grünwald and Gram methods help to differentiate between the different forms of cells. Sternal puncture and lymph node or tumor imprints are diagnostic aids, and the hematologist is a consultant required by most dermatologists to recognize the cell types upon which critical diagnosis depends. The recognition of leukemic eruptions of the skin as often depends on discovery of the abnormality of the blood count as vice versa. One should biopsy every suspected case irrespective of the blood findings. Exfoliative dermatitis due to lymphoblastoma can be distinguished from psoriatic or inflammatory erythroderma by this means

Cases of allergic dermatitis simulating lymphoblastoma were interestingly presented by Cannon (ADS 39 846 1939) The difficulties of diagnosis were well portrayed by the illustrative cases of Goldsmith (BJD 56 107 1944)

The utilization of cutaneous smears in diagnosis was discussed by Wilson (JID 22 178, 1954) who found the technic capable of providing cells of dermal infiltrate in an undistorted state so that the findings might be more specific than those obtained by study of the usual sections. The freshly cut skin was impressed upon glass slides, and the material was air-dried and treated with Wright's stain for 90 sec., then with a buffer solution for 5 min., after which it was washed and dried.

The incidence of leukemia in radiologists appears to be some 8 times as high as in persons whose occupations do not result in exposure to ionizing radiation (Ulrich: NEngJM 234 45 1946)

A family in which 5 of 8 siblings had leukemia in early childhood was reported by Anderson (AmJDisChild 81 313 1951)

Attempts to inoculate leukemia cells from one human being to another failed when tried by Thiersch (JLabClinM 30: 866 1945) There is no evidence that leukemia can be transmitted from mother to fetus (Allan BMJ 2 1080 1954); patients with chronic leukemia survive pregnancy and parturition, but may collapse soon afterward with extension of the leukemic process.

Surveying 647 Scottish cases, Gauld et al. (BMJ 1: 585, 1953) reported that the commonest type was chronic lymphatic, followed in order by chronic myeloid, acute lymphatic, acute myeloid and monocytic types. One fifth of them were aleukemic, a characteristic seen most often in acute forms and most seldom in chronic myeloid cases. While the age incidence conformed to that reported by others, acute myeloid and monocytic forms showed a wider range than in figures generally quoted. The peak age incidence of chronic lymphatic leukemia was from 60 to 70 years, and of chronic myeloid from 45 to 50 years, while acute lymphatic occurred by predilection in the first 5 years. While predominant occurrence in males was noted in chronic lymphatic leukemia it was less obvious in other types. There appeared to have been a two-fold increase in over-all incidence during the period of the survey from 1938 to 1951.

A preleukemic phase preceding the development of true leukemia was described as found in 12 patients by Block et al. (J 152: 1018 1953) One or more types of marrow dysfunction were discovered, most commonly a hemorrhagic tendency usually accompanied by thrombocytopenia. Neutropenia was found comparatively early and preceded the disappearance of small lymphocytes. Monocytosis was fairly common but was hard to evaluate because of the difficulty in differentiating these cells from myelocytes. Erythroblastosis and reticulocytosis, sometimes of spectacular degree, were common. Immature cells tended to appear in the peripheral blood toward the end of the preleukemic phase but peripheral blood characteristic of acute leukemia was first seen in the leukemic phase. In the preleukemic phase the most characteristic early change in the marrow was the development of arrest of maturation and aplasia of granulocytes, accompanied by erythroblastic tissue changes varying from aplastic to extremely hyperplastic. Thereafter, progressive hyperplasia and maturation arrest of granulocyte precursors developed until the marrow was largely replaced by stem cells and promyelocytes; this marked the beginning of the leukemic phase. Examination of the few available liver and spleen biopsies in the preleukemic phase failed to reveal any marked abnormality. Occasional stem cells were seen in the splenic red pulp immediately prior to the development of the leukemic state. The major problem in differential diagnosis was the resemblance of the preleukemic state to various blood dyscrasias, especially toxic neutropenia, aplastic anemia, or hypersplenism. This problem in differential diagnosis was not clarified until there developed the leukemic state which was almost invariably acute and, in some cases, explosive.

Prognosis.—In the majority of cases of myelogenous and monocytic leukemia, life continued for a month or less after the development of cutaneous tumors; the median duration of life in all cases of leukemia was 6 months (Gates, 1938) Mycosis fungoides and Hodgkin's disease may exist for years. Leukopenia anemia and bleeding are bad signs. In all cases except lymphocytoma, death may be expected.

Among 8 cases of chronic myeloid and 40 of chronic lymphatic leukemia studied by Leavell (AmJMedSci 196: 329 1938) expectancy averaged 3.5 years, but in those with skin lesions it ranged from 1 to 1.6 years from the time cutaneous manifestations appeared. Of bad omen were severe anemia, low white blood cell count, and bleeding

In 172 patients with acute leukemia, ranging in age from 2 months to 73 years, Southam et al. (Canc 4: 39 1951) reported a mean survival time from the onset of symptoms of 20.3 weeks, the longest being 68 weeks. Half of the patients were dead within 1? weeks, and 90% of them within 36. X ray nitrogen mustards, radioactive phosphorus and urethan were all without significant therapeutic effect, but antibiotics and transfusions appeared to increase survival time slightly

The prognosis for survival in chronic granulocytic and lymphocytic leukemia was intensively studied by Harold Tivey whose figures were based on observations of over 1,500 cases. There was no significant difference in prognosis between lymphocytic and granulocytic leukemia. He communicated to me the following data in January 1954

Survival	Patients	Median Survival Time	Confidence Limits
Duration from onset of symptoms	1,978	2.65 years	2.55 2.75 years
Duration from first therapy	651	1.56 years	1 44 1.70 years
The corresponding more recent figures for the series of Drs. Osgood and Seaman on cases treated with small doses of x ray therapy are:			
Duration from onset of symptoms	163	4.2 years	2.5 -5.6 years
Duration from first therapy	163	2.3 years	1.9 –.7 years

** Confidence limits show the range of median survival times expected statistically from 95 of 100 series of size and composition similar to those studied.

Treatment.—Good results in leukemia have been known to follow the administration of benzene a leukocyte poison. Arsenic may benefit, and arsphenamine in small doses has proved helpful in a few instances. Radiotherapy over skin, lymph nodes or the long bones with frequent checking of the white cell count may yield excellent results for a time (Murphy J 115 1556, 1940 Dowdy and Lawrence J 116 2827 1941) Substances rendered radioactive by use of the cyclotron are of value when given orally in doses guided by blood findings (Warren NEngJM 223 751, 1940) P^{32} prolonged comfortable life, and its administration did not produce radiation sickness, but did not result in any marked improvement in survival in the 129 patients with chronic myeloid leukemia studied by Lawrence et al. (J 136 672, 1948 140 65?, 1949) Transfusions antibiotics and other palliative efforts are used.

See Hamilton and Stone (Radiol 28 178, 1937), radiosodium Levitt (Lancet 1 ?, 1940) x-ray baths Howes and Levin (Radiol 40 ?, 1943) recommending large doses in primary Osgood (AIntM 87 329 1951) in ore small doses of radiation Osgood and Seaman (J 150 1372, 1952) statistical proof that x ray therapy in small doses is best.

Chemotherapy of Malignancy with discussion of urethan, vitamin antagonists nitrogen mustards, TEM, cortisone and ACTH, and other hormones was reviewed by Reinhard et al. (J 142 383 1950) and by Gellhorn (CancRes 13 205 1953) Only a few types of tumors are responsive to drugs, and all but the hormones are significantly toxic to normal as well as neoplastic cells. Rundles et al (SouthMJ 46 259 1953) felt that urethan is the most effective agent presently available in multiple myeloma NH_2 and TEM are useful especially in Hodgkin s disease and lymphoid proliferative disease TEM is the drug of choice in chronic lymphoid leukemia ACTH and folic acid antagonists are capable of sometimes producing temporary remissions in acute leukemia and ACTH and cortisone are not valuable in chronic leukemia or lymphoma unless accelerated hemolysis of the red cells is present

The good remissions in leukemia in both children and adults obtained with ACTH by Pearson et al. (CancRes 10 235 1950) were incomplete and lasted for only a few days. A notable remission in 1 patient with monocytic leukemia was obtained with ACTH by Kinsell et al. (J 144 617 1950) who persisted with high dosage and with adjunctive transfusions. Remissions of from 3 to 13 weeks were obtained with ACTH and cortisone in several children with acute leukemia by Snelling et al. (Pediat 8 22, 1951) Remissions occurred in

about half the children treated by Darte et al. (CanadMAJ 65 560 1951) The drugs were assessed as having little practical value by Cameron et al. (CanadMAJ 65 552, 1951) Cortisone did more for children with acute lymphatic leukemia than for those with myeloid, in the experience of Fessas et al. (AIntM 94 384 1954)

Acute leukemia may be be fited by 6-mercaptopurine a substance discovered in the course of investigating different types of desoxynucleic acid, reported Rhoads (Sci 119 7" 1954) It may be that chemicals can be designed to injure certain cells selectively ACTH and cortisone in conjunction with 6-mercaptopurine were capable of affording several months of useful life in cases of Fountain (BMJ 1: 1119 1955) while 6-MP was of low toxicity as compared with aminopterin, and its use gave remissions in a third of the acute leukemias in children even after other chemotherapeutic agents had failed, although it was less helpful to adult patients reported Bernard and Seligmann (SemHôpParis 30: 2971 1954)

Ethyl carbamate (urethan) acts favorably seemingly because of a strong selective suppression of mitosis of pathologic cells (Moeschlin: abs J 135: 390 1947) Dustin (abs J 135: 741 1947) gave 4 Gm. t.i.d. to 8 patients with chronic myeloid leukemia with con siderable general improvement. It can produce a ma ked fall in white cell count, and thereby apparently caused the death of a patient of Webster (J 135: 901 1947) It was first shown inhibitory to tumor growth by Haddow and Sexton (N ture 157: 500, 1947) It has use particularly in chronic myeloid cases, but acute leukemias are little influenced by it (W lson et al. JKanaMS 49: 97 1948)

Aminopterin, a folic acid antagonist, may yield temporary remission in acute leukemia, with survival in some cases far beyond what might be expected without it (Farber: Blood 4: 160 1949; Dameshek ib p. 168) but it does not cure The dose may be given as 1 mg daily by mouth or intramuscularly until toxicity is evident (Sti kney et al.: PSMMC 24: 525, 1949) It has been known to cause exfoliative dermatitis and alopecia as well as nausea, hemorrhages and ulceration of mucosae, nd its effects may be assumed as unpredictable (Meyer et al.: CancRes 9: 606, 1949; AmJClinPath 19: 119 1949) Its use is discussed also in the treatment of psoriasis (p. 933)

See Robey and Russell (NEngJM 235: 585, 1947) lymphatic leukemia temporarily helped with estrogenic substances; Hirschboeck et al. (J 136: 90, 1948) urethan disappointing; Rottino (Canc 3: 272, 1950) adenylic acid relieved pruritus in Hodgkin disease Sacks et al. (AnnIntM 32: 80, 1950) folic acid antagonists; Dacie et l. (BMJ 1: 1447 1950) Aminopterin helped 9 of 13 cases of leukemia; Oster et al. (NEngJM 243: 984, 1950) urethan toxicity; Spies et al. (South MJ 43 497 1950) beneficial effects of ACTH.

Chemotherapy of Cancer.—See Shear (AmJCanc 33 44, 1938) chemical treatment of tumors; Hahl et al. (AmJHyg 36D 224, 1942) bacterial toxins, effects; N wts et al. (Canc Res 6 305, 1946) bacterial toxins; Reilly (CancRes 13: 821, 1953) microbiology and cancer therapy review and bibliography; Burchenal (CancRes 14: 615, 1954) chemotherapeutic agents singly and in combinations in clinical use; Galton and Till (Lancet 1 425, 1955) 1 4-dimethanesulfonyloxybutane—Myleran—maintenance therapy in chronic myeloid leukemia.

The Nitrogen Mustards particularly of war gas chemicals, have an action on nucleoprotein resembling that of x-rays (Gilman and Philips: Sci 103: 409 1946) Goodman (J 132 127 1946) reviewed 67 cases treated with such chemicals, and Jacobson et al. (J 132 263, 1946) reported 59 patients with diseases of the hematopoietic system who were given methyl bis (beta-chloroethyl) amine hydrochloride in doses of 0.1 mg. per kg in courses of from 1 to 7 daily injections. The margin of safety was narrow but serious toxic effects, such as granulocytopenia, thrombocytopenia and anemia, were avoidable by a safe dosage schedule. Less consequential side effects included pain on injection, thrombosis of injected veins, vomiting, malaise anorexia and headache. Benefit was greatest in Hodgkin's disease, lymphosarcoma, and chronic leukemia, with sometimes dramatic improvement in lymphadenopathy splenomegaly and hepatomegaly Acute leukemia and multiple myeloma did not respond.

Cases no longer responsive to x ray therapy may respond to these chemicals, and relapses after nitrogen mustard treatment have responded to further treatment with the agent. Cure is not btained, benefits resemble those induced by radiation, and optimum dosage has not been worked out. Utility is especially noteworthy after radioresistance has developed, reported Osborne et al. (J 135: 1123, 1947), who tried it with purported benefit in chronic disseminated lupus erythematosus. Toluidine blue intravenously was n effective antidot for the anticoagulant effect of the drugs, reported Smith et al. (Sci 107: 474, 1948) Nitrogen mustards are not useful in early localized forms of lymphoblastoma, where radiation in about the maximum dose the skin can tolerate was pref rred by Craver (J 136 44, 1948) H estimated that "even when Hodgkin's disease or lymphosarcoma begins to generalize by and large roentgen irradiation is a more effective agent than any of the nitrogen mu t rds that have been tried."

M thyl-bis (HN), the most widely used preparation, appeared particularly helpful in severe cases of Hodgkin's disease with constitutional symptoms nd visceral involvement sometimes achieving complete rehabilitation and an increase of life span of from se eral months to years, according to Dameshek et al. (Blood 4 335 1949) While the effect on mycosis fu goides may be dramatic, with better relief of pruritus than is afforded by x-ray therapy, the ultimate prognosis is not improved, according to Goldberg and Mason (ADS 60: 181, 1949)

Triethylene melamine (TEM) given by Rottino in a dose of 5 mg before breakfast once or more times weekly produced no immediate toxic effect but sometimes caused nausea, anorexia, vomiting and depression of bone marrow occasionally extreme. Results in his 94 various cases were impressive in lymphatic leukemia, less so in lymphosarcoma and chronic myeloid leukemia. In Hodgkin's disease the results varied. The side effects seemed less intense than those of NH to Bond et al. (AIntM 91: 602, 1953) 18 of their *26 cases of chronic myeloid leukemia were rehabilitated from invalidism to productive living*. Tolerance of the drug was proportional to the white blood cell count. The effects in Hodgkin's disease seemed less favorable than as reported by others. TEM seemed futile in monocytic leukemia, but it satisfactorily controlled chronic myeloid and lymphatic leukemias. Pruritus in Hodgkin's disease responded well but generally only temporarily in the patients of Paterson et al. (BMJ 1: 59 1953)

See Lalit (J 135 93, 1947) Philpott et al (J 135 631 1947) Taffel (YaleJBiol 19 971, 1947), not curative in 16 cases, but beneficial in 1 case of mycosis fungoides; Karnofsky et al (JID 9 196, 1947) 6 cases, 4 of which had become radioresistant, with benefit but some severe reactions. Apthomas and Cullumbine (Lancet 1: 899 1947) palliative in 21 cases of Hodgkin's disease. Wintrobe (AnnIntM 27 529 1947) dosage and technic of administration. Henstell and Tober (JID 8 183, 1947) striking, prompt improvement, mycosis fungoides. Block and Murphy (APath 46 519 1948) mycosis fungoides, skin healed, patient died in leukopenia, jaundice and hemorrhagic state; Zanes et al. (JLabClinM 33: 1002, 1948) benefit in 20 of 31 cases, Hodgkin's. Sherry (SouthMJ 41 110, 1948) benefit in Hodgkin's, none in lymphosarcoma or melanoma; Faloon and Gorham (NYSJM 48 612, 1948) methyl bis helpful in Hodgkin's and polycythemia vera. Nabarro (BMJ 2 622, 1949), perhaps better than irradiation in widespread lesions in ointment; Rosenthal and Kaplan (AmJSurg 81 13, 1949) palliative only x-ray preferred in early local forms. Kurnick et al. (AnnIntM 30: 1 1949), methyl bis in 64 cases, brief remissions in 20 of 34 Hodgkin's cases, some in bronchogenic ant. Shullenberger et al. (J 139 773 1949) 18 advanced, Hodgkin's, transient, limited usefulness. Spurr et al. (AmJMed 8 710, 1950) 95 cases, useful adjunct; Alpert et al. (AnnIntM 32 393 1950) no significant benefit in reticulosarcoma, chronic lymphatic or subacute myeloid leukemia, serious complications. Osgood and Chu (CancRes 10 38, 1950) marrow-culture studies showing difference of action from radiation, colchicine or urethan, stopping differentiation. Sweitzer et al. (ADS 61 13, 1950) treated patient died quickly. Gellhorn and Collins (AnnIntM 35: 1250 1951) 132 Hodgkin's cases, comparing NH and x ray with x-ray alone. *NH gave subjective improvement, reduced x ray dosage needed*, did not prolong expectancy. Rose et al. (YaleJMonth 79 562, 1952) combined nitrogen mustard and x ray, dubious improvement. Rundles (GP 9 76, 1954) individualization of dose in using TEM, narrow margin between therapeutic and toxic.

EOSINOPHILIC GRANULOMAS

A variety of granulomatous lesions, if containing a conspicuous number of eosinophilic leukocytes, have become known as eosinophilic *granulomas* during the last 13 years. Pinkus (MedClinNoAm 35 463 1951) wrote. He concluded that the various lesions so described are a heterogeneous assembly and that the term as used at present has no diagnostic significance without qualification.

Eosinophilic granuloma of the skin was the title first used to designate 3 human cases by Nanta and Gadrat (BsocfrançD 44 1470 1937) and miscellaneous cases were soon thereafter published under this caption. The various dissimilar dermatologic lesions were classified by Weidman (ADS 55 1947) into lymphoblastomatous and symptomatic inflammatory forms. The disease is not an entity but only a histologic syndrome he stated. His blastomatous class contained (a) cases, *if they should appear* of hypothetical eosinophilic aleukemic myelogenous leukemia (b) endotheliosis with eosinophilia which was his interpretation of the penile lesions of the patient of Robinson and Ketron, and (c) reticuloendotheliosis with eosinophilia such as has occurred in Hodgkin's disease mycosis fungoides and other lymphoblastomas. His symptomatic class included eosinophilic granulomas of the skin when they occur in (a) erythema multiforme perstans (*Loeffler's syndrome*) (b) eosinophilic periarteritis (c) erythema elevatum diutinum (d) tuberculosis cutis orificialis (e) various specific and nonspecific granulomatous inflammations such as that associated with *T purpureum* infection in the case of *Lewis* and Cormia (ADS 55 176 1947)

The classification of Pinkus (1951) was similar. Among the symptomatic examples he included the persistent lesions which *may follow* arthropod bites (Allen: AmJPath 24 367 1948) and other foreign body granulomas, and his granuloma faciale and the cutaneous manifestations of eosinophilic granuloma of bone. Lever and Leeper (ADS 62 85 1950) and Pinkus (1951) concurred in extricating from the Babylonian confusion only 2 well-defined

clinicopathologic syndromes (1) benign reticulogranulomas forming ulcero-vegetative plaques on the skin and mucous membranes often in combination with less characteristic skin lesions and with lesions in other organs, particularly in the bone, being related to Hand-Schüller-Christian and Letterer Siwe syndromes and (2) a form aptly called by Pinkus granuloma faciale, shown by patients who exhibit slowly-growing indolent, therapy resistant lesions of papular and nodular character located almost exclusively on the face.

Granuloma Faciale—Reddish, brownish or purplish in color the lesions begin as macules and progress so as gradually perhaps even to cover large parts of the face They are single or multiple soft or moderately firm to the touch, never ulcerate are often mistaken for sarcoid or lupus erythematosus, affect adults, and are not associated with significant systemic disease. They show histologically in the upper half or two-thirds of the dermis, a mixed inflammatory infiltrate of lymphocytes, plasma cells histiocytes and polymorphonuclear leukocytes, of which a variable proportion are eosinophils. As the number of cases of granuloma faciale increases, their remarkable similarity among each other becomes more and more apparent. The histologic picture *can be said to be diagnostic, but the clinical features become highly suggestive* to an observer who has seen several cases. Even in this clinicopathologic entity the factor of eosinophilia is of secondary importance Pinkus believed.

The granuloma faciale type constituted 4 of the reviewed cases and 3 of those seen by Lever et al. (ADS 58: 430, 1948) and presented a uniformity of appearance and structure being sharply defined, slightly raised, purplish plaques covered by normal epidermis, of soft and elastic consistency with a few nodular irregularities in the large ones, asymptomatic, slowly enlarging, and numbering from 1 to 5 lesions altogether Seven cases were described by Pinkus (Dermatologica 105: 85, 1952) Spontaneous involution is rare although these cases do not ulcerate. The age range was from 31 to 69 years. Neither sex was preferred. Lacking radiosensitivity, the disease can be cured only by excision. It has been known to recur in a graft. It may involute slowly with fibrosis and resolution of inflammation.

Eosinophilic Granuloma of Bone (Benign Reticulogranuloma)—Lichtenstein and Jaff (AmJPath 16 595 1940) gave the name "eosinophilic granuloma to certain destructive but relatively benign osseous lesions, which were recognized by Green and Farber (JB&Surg 24. 499, 1942) as mild manifestations of pathologic processes known in their severe forms as Hand-Schüller-Christian and Letterer-Siwe diseases (q.v) Cases have been reported in which there were associated granulomatous lesions of the skin. Curtis and Cawley (ADS 55: 810 1947) described an infant with such involvement and considered the relation of the coalescing red papules on the buttocks, genitalia and elsewhere to the osseous lesions. The skin lesions in their patient cleared after x ray therapy was given the bone lesions.

In benign reticulogranuloma, 4 types of lesions have been found (Cobane et al.: ADS 61: 442, 1950) (1) small, yellowish or brown, keratotic papules, resembling those seen in Letterer-Siwe disease and consisting of small accumulations of histiocytes and monocytes which cluster around the papillary vessels and may invade the epidermis; (2) patchy dermatitis, mainly on the scalp, resembling seborrheic dermatitis and similar to the dermatitis found in systemic, progressive reticulogranuloma and consisting of moderately dense granulomatous accumulations of histiocytes (3) granulomatous, often ulcerated, plaques, mainly in the genital region; and (4) sinus tracts and ulcers due to extension of deep granulomatous lesions showing histologically the changes of benign reticulogranuloma of bone. These manifestations are not at all similar to granuloma faciale.

Syphiloid.—There is a contagious disease of cats, with eosinophilic granulomatous lesions. In these animals the name is applicable to a disease which "satisfies all the criteria for an entity etiologic, clinical and histologic" (Weidman ADS 56: 165 1947) Since several cases of the human disease have involved the lips, vulva or anus, the possibility of transmission from cats to human beings must not be forgotten. The perianal and peribuccal lesions of the original patient of Nanta and Gadrat were indistinguishable from syphiloid of cats Pautrier is said to have said. Compare Cat scratch disease.

Asked about "syphiloid" in cats, Kral, co-author with Novak of Veterinary Dermatology (Lippincott, 1953) wrote me in January, 1954. "The term 'rodent ulcer' has been used for that disorder Rodent ulcers or labial ulcers are best described as a chronic ulceration of the upper lip occurring at the junction of the upper lip and mucous membrane. Biopsy usually indicates chronic inflammation with subsequent fibrosis. Walpers (Veterinary Record 61 671, 1949) found staphylococci present in most cases. Kirk referred to them as 'basal cell carcinomas, but McGrath found only chronic ulcerative inflammatory changes. These lesions respond poorly to x-ray therapy If the condition is seen early before it becomes too extensive, surgical removal and cauterization may be attempted. Topical applications of 1% aqueous gentian violet may benefit. I did not mention 'rodent ulcer' in cats in my Dermatology because the etiology is still not definitely known, and it occurs relatively very rarely However spirochetosis is one of the common infectious diseases in rabbits.

ALLERGIC GRANULOMAS WITH AND WITHOUT EOSINOPHILIA

Loeffler's Syndrome and Allergic Granuloma.—Loeffler (BeitrKlinTuberk 89 368 1932) described a syndrome characterized by transitory pulmonary lesions, remarkable eosinophilia of the blood, and a clinical course that was mild as compared with the abnormalities in chest films (see Lehman SouthMJ 41 40 1948) Fever was variable but usually absent. There was some asthenia The duration of the illness was from 8 to 10 days as a rule. Chest films showed well-defined areas of infiltration, generally in the lower lung fields single or multiple unilateral or bilateral, often completely resolving within 1 week. Auscultation revealed little or no change Slight pleuritic pain might be present. Sputum was small in amount or absent. Histologic findings were not characteristic, but simulated bronchopneumonia, and eosinophils might comprise from 70 to 100% of the inflammatory cells. Loeffler et al. (abs J 138 925 1948) found that, while ascariasis is sometimes the cause it is not invariably so although helminth infections are often present (Hodes and Wood AmJMedSci 210 288 1945) Yet the mechanism appears to represent hypersensitization of the vascular system to extrinsic allergens, the small vessels of the lung serving as shock tissue (Barden and Cooper Radiol 51 44 1948) The phenomenon has occurred as a manifestation of penicillin intolerance (Falk and Newcomer J 141 21 1949)

Allergic Granulomatosis was segregated as a clinical and pathologic syndrome occurring in individuals with an allergic background by Strauss et al. (JID 17 349 1951) Not only do the pulmonary tissues participate in the Loeffler phenomena but also the cardiac, gastrointestinal, renal, nervous and cutaneous. Skin manifestations are of frequent occurrence in allergic granulomatosis according to Strauss et al. who found them in 19 of 28 cases, wherein the illness ran a subacute or chronic course of from 3 months to 5 years or more with remissions and exacerbations. The mortality was high when there was systemic involvement of the blood vessels.

NODULAR DERMAL ALLERGIDES (MALADIE TRISYMPTOMATIQUE) OF GOUGEROT—The syndrome is characterized by an eruption consisting of 3 associated lesions (1) small, round nodules, a few mm. in diameter within, under or slightly projecting from, the dermis, circumscribed, firm normal in color or slightly rosy without peripheral edema (2) purpuric macules of 1 to 5 mm. diameter and (3) erythemato-papular elements 2 to 10 mm. in diameter or rarely larger resembling the lesions of erythema multiforme *Occurring for* the most part in adults, the eruption is generalized but is most profuse on the legs, where there may be hundreds of lesions. Individual attacks mark its evolution, clearing taking place without sequelae in from 15 to 60 days. Pleomorphism of the eruption is marked, but occasional cases show only nodules or only nodules with purpura, or nodules with urticaria. Rarely a case presents bullous or necrotic lesions, too or both. All the lesions are relatively painless Itching is inconstant. Sometimes the attacks are associated with fever fatigue arthralgia and headache but the general health remains good even though the disease may recur over a period of many years.

Histologically the changes are largely in and about the arterioles and capillaries. Endothelial swelling may obliterate small vessels. Perithelial cuffing with fibrinoid necrosis is seen. An inflammatory infiltrate lies around the areas of fibrinoid necrosis and extends into the surrounding zone The infiltrate is mainly polymorphonuclear leukocytic, with pyknosis of some nuclei. Eosinophils are rare

Treatment that is dependably effectual was not known to Gougerot and Duperrat (BJD 66 283 1954) who considered the condition to be the mildest form of cutaneous allergic disorder of which polyarteritis nodosa is the most severe and lethal type and of which the granulomatous vascular allergides of Strauss Churg and Zak are a fairly serious variety Cortisone ought to be helpful ACTH was (Kesten and Jackson AD 72 194 1955)

Allergic Cutaneous Arteriolitis was described on the basis of 2 cases characterized by severe allergy fever and eosinophilia, accompanied by systemic manifestations (vascular cardiac, pulmonary gastrointestinal, renal and cutaneous) by Ruiter (BJD 66 174, 1954) the skin exhibiting scattered erythematous lesions on the extremities suggestive of allergic granulomatosis.

Three groups of dermatologic changes were segregated: (1) erythematous maculopapular eruptions resembling erythema multiforme (2) hemorrhagic lesions ranging from petechiae to extensive ecchymoses, sometimes with necrosis and often associated with urticaria, comparable with Schoenlein's purpura and (3) cutaneous and subcutaneous nodules. Several types of lesions might occur in one patient at the same time. Lesions tended to appear in crops and to show exacerbation and remission. In healing there was no scar unless necrosis had taken place. The common sites were the extensor and flexor aspects of the extremities. Subcutaneous nodules, when found, were generally on the extremities or scalp, rarely on the trunk.

This syndrome of severe allergy fever and eosinophilia, accompanied by systemic manifestations, was manifested histologically by granulomatous inflammation with marked eosinophilia, which in its most typical form produced, they said, a nodule composed of severely altered connective tissue and necrotic exudate surrounded by histiocytes and giant cells. The relation to periarteritis nodosa was discussed.

Multiple granulomas with noduloulcerative lesions of the face and extremities and also systemic involvement were seen in 2 patients by Welsh and Altemeier (ADS 61: 619 1950) whose studies were exhaustive; but the cause and classification of the disease could not be determined.

Keratogenous and pigmentary dermatitis with bullae and eosinophilia was seen in 4 newborn girls by Asboe-Hansen (ADS 67: 152, 1953) in a period of a few years in Copenhagen. Papules, vesicles and pustules with a tendency to form groups localized particularly on the extremities were the notable cutaneous feature. Eosinophilia of the blood diminished if and when skin lesions healed. Verrucous keratoses formed at the sites of vesicles in the course of healing and were later shed, leaving brown pigmentation and atrophy The description allows one to think of a relationship to reticulogranuloma and Letterer-Siwe disease.

One rather expects medical essays in the near future to attempt correlation of scores of conditions wh rein various admixtures of "collagen disease, allergic granulomatosis, reticuloendothelioses, stress phenomena, Loeffler s syndrome, Shwartzman s phenomenon, systemic lupus erythematosus, periarteritis nodosa, certain xanthomatoses, and forms of misery to which the human body is subject but of which we have not as yet heard will be commingled inextricably One takes comfort in the fact that the human mind is almost as constrained as the molecules f molten metal to find order in the uni v rse: crystals will evolve but the melting pot is as yet quite warm.

See Martinotti (DWchn 112: 25, 1941), 2 cases Cerutti (Dermatologica 85: 90 1942) case with Hodgkin's disease; Lewis (ADS 49 275, 1944), case, plaques on thigh; Bailey (JID 7: 201 1946) facial case; Dobes and Waldman (ADS 55 212, 1947) Hodgkin case with extreme eosinophilia Lever (ADS 55 194, 1947) facial case, review discussion of relationships; Lever (ADS 57 656, 1948), facial case resembling erythema elevatum diutinum McCreary (ADS 58: 272, 1948), child with tumors and ulcers of upper trunk and scalp since rumps t age 2; Collins (BJD 59: 22, 1947) woman groin, solitary tumor Oliver et al. (ADS 60: 701, 1949) 2 cases; Oliver and Lorant (ADS 60: 872, 1949) facial case; Adams and Kraus (ADS 61: 957 1950), old woman with skin and lung lesions, obliterative arteritis, necrosis and eosinophilia. Lever (ADS 62: 466, 1950) forehead lesion; Borrie (BJD 62: 236, 1950) brown nodules in lower eyelids; Woerdeman (Granulomata Eosinophilica Cutis, Amsterdam, 1951, 220 pp.; also BJD 64: 42, 1952) monograph; Peck et al. (ADS 65 214, 1952) 2 facial cases; Kalkoff and Dietz (DWchn 126: 661, 1952) facial Henderson and Thompson (J 151: 294, 1953), case, jaw and lung involvement, no response to corticotropin; McKay et al. (BGO 66: 437 1953) 3 vulvar cases; Woerdeman and Prakken (Dermatologica 108: 133, 1954) classifications; Mark (DigChest 25: 128, 1954) 22 cases Loeffler's syndrome, only 3 with metazoan parasites, eosinophilia maximum just prior to recession f pulmonary lesions Steigleder and Elschner (DWchn 130 878, 1954), 2 eosinophilic granulomas at angles of nose and in mastoid region; Dawes (JLaryngol 68 675, 1954) 6 cases illustrating otologic aspects of eosinophilic granuloma, Letterer-Siwe disease and Hand-Schüller-Christian disease; Foreign Letter Vienna (J 160: 317 1956) autopsy of boy showing relation of eosinophilic granuloma and Letterer-Siwe disease.

METASTATIC TUMORS IN THE SKIN

Secondary Neoplastic Infiltrations in the Skin are of considerable biologic and diagnostic interest. Metastases may reach the skin by (1) invasion by extension via tissue, blood and lymph spaces (2) lymphatic embolism; and (3) hemic embolism. See Squamous cell carcinoma metastasis (p. 1202) and pathology (p 1218); also Willis (The Spread of Tumours in the Human Body Mosby 1952, p. 276 ff.)

Invasion is exemplified most commonly by mammary cancer and by growths in the cervical or inguinal lymph nodes. By stretching and thinning, the dermis may long resist perforation. When this occurs, exuberant fungation is the rule. Cancers originating in the mouth, cervix uteri, larynx and penis and melanomas may produce similar satellites. Outcrop nodules, often lentiform or plaquelike, are frequent in the skin in the neighborhood of mammary cancer. In advanced cases they may be found in large numbers over





Fig. 1788.—Carcinoma en cuirasse with lenticular outcrop nodules and lymphedema of left arm. (Dr. Howard Morrow.)
Fig. 1789.—Inflammatory carcinoma of breast, extremely rapid in progress.





Fig. 1790.—Carcinoma en cuirasse sclerosing 10-year duration. (Dr. Harold N. Cole.)
Fig. 1791.—Inflammatory carcinoma of face and neck, originating from rectal primary. (Reut and Nomland: Wis. M. J. 40: 186, 1941.)

the entire trunk and in smaller numbers on the proximal segments of the limbs and on the head. Umbilical nodules may appear in this manner as a result of extension from cancer of the stomach, gall bladder, intestine, ovary or uterus (Cullen: The Umbilicus and Its Diseases, Saunders, 1916, p. 402).

Extension via vascular channels may consist in inconspicuous permeation or in redness, tenseness and burning sensations, as in inflammatory carcinoma of the breast, or in nodules or plaques formed by outcropping of the permeated

tions of the deep fascial plexus or in cancer *en cuirasse* (Reuter and Nomland WiscMJ 40 190 1941) Carcinoma *en cuirasse* may be manifested by small, flattish papules usually rising slightly above the *niveau* carcinoma lenticulare. Discrete at first, they coalesce to form leathery induration (eburnated



Fig 1792.—Metastatic carcinoma from thymus, in newborn. (Wasserman: J Pediat 14 788, 1939.)





Figs. 1793A and 1793B.—Meningioma eroding through skull, producing immense scalp tumor and histologic structure. (Layman and Becker ADS 39 626, 1949.)

carcinoma of Alibert see Schreiner and Volavsek AfDuS 174 22, 1936) The commencement may be morphea like, or marbling may appear with only slight induration. Progress is usually slow but the telangiectatic type may go fast (Savatard: BJD 55 31 1942)



Fig. 1794.—Recurrence of squamous carcinoma in scar of operation intended to remove cervical lymph node metastases of cancer of the lip.





Fig. 1795.—Hematogenous metastases of hypernephroma. (Dr. Sam Sueltzer.)
Fig. 1796.—Metastases from prostatic primary. (Ronchese, ADS 41: 438, 1940.)





Fig. 1797.—Squamous carcinoma [illegible] wen, with metastases in scalp and lymph nodes.
Fig. 1798.—Outcrop nodules of buttock, carcinoma of rectum. (Dr. T. W. Abernethy.)

Erysipelas-like, fulminating breast cases are due to invasion of arterioles by tumor cells (Dawson and Davie: EdinMJ 49: 247 1942) The 8 cases of Dawson and Shaw (BritJSurg 25 100 1937) all showed extensive adenopathy and in the skin was found proliferation of cancer cells which were within the capillaries evidently as the result of arterial embolism. Dawson and Shaw thought the phenomenon not a distinct pathologic entity for it varies in rate of advance may or may not be associated with Paget s disease of the nipple and merely signifies advanced disease. Of 885 breast cancers, 4% were of this type, as reported by Taylor and Meltzer (AmJCanc 33 33 1938) who noted the rapidly progressive nature of the lesion with early visceral metastasis, its



Fig. 1179.—Inflammatory carcinoma of the breast (Dr John C. Delmario.)



Fig. 1180.—Metastasis of inflammatory breast carcinoma into terminal rterioles of the skin. Carcinoma cells are within endothelium-lined spaces. (Dawson and Shaw BJS 25 100, 1937)

occurrence in large fatty breasts, and the palliative effect of x ray in contrast with the futility of surgery as a rule. Adrenalectomy was remarkably beneficial in a patient of Eckert (pers. comm., 1955)

Skin recurrences followed breast operation by 8 to 18 months despite post operative radiation, in the experience of O'Brien (Radiol 30 407 1938) and the speed of their appearance seemed related to the extent of the growth at the time operation was done He felt that it would be wise to administer large amounts of radiation before operation, at a time when the skin would tolerate it, rather than afterward, when x ray would not prevent recurrence anyway The patient of Freeman and Lynch (ADS 35 643 1937) developed telangiectatic and cystic lesions in the diffusely infiltrated skin of a carcinomatous breast.

Lymphatic Obstruction may give rise to edematous elephantiasis of the part. Gangrene of the skin may result as in a patient with carcinoma of the lung reported by Le Fort et al. (Annd anatpath 15 59 1938) Angiosarcoma (p. 1122) has appeared in several cases of postmastectomy lymphedema (Jenner et al. ADS 65 123 1952)

Lymphatic Embolism is probably the usual way in which carcinoma and melanoma cells reach the regional lymph nodes. This is the only route that is important in operable cases of carcinoma (Gray BritJSurg 26 462, 1939) Melanoma may metastasize by way of either the blood or lymph channels.

Hematogenous Skin Metastases are not likely to be present until extensive visceral metastasis has already taken place The incidence of skin secondaries was 2 7% in 2,300 autopsies reviewed by Gates (AmJCanc 30: 718, 1937) Of the epithelial growths half had originated in the breast. No tumor she thought shows real predilection for cutaneous metastasis. Skin lesions of the lymphosarcomas (q v) are usually metastatic lesions though of course some are primary There is no sharp dividing line between the so-called exanthems and the true cutaneous tumors in the leukemias. These are the result apparently of merely fortuitous localization of diffusely disseminating cells Zosteriform distribution of metastases has been observed Wenlike lesions of the scalp may in reality be metastases from distant cancerous organs (Montgomery SurgClinNoAm 17 1249 1937)

Living cancer cells transferred by the blood stream may reach the skin from a primary source anywhere in the body In many cases with widespread dissemination however the skin escapes but in some instances the growths appear in the integument while the viscera are affected to a lesser degree or not at all Melanoma frequently evinces dermal preference The lesions are few or many and widely distributed The usual forms of cutaneous secondary lesions Gates noted are expanding intradermal or subcutaneous nodules or plaques, generally firm smooth and comparatively asymptomatic. Gastric intestinal mammary pulmonary vesical renal uterine and thymic carcinomas have been reported among the numerous possible primary tumors, and lymphosarcoma myosarcoma osteosarcoma and hypernephroma have likewise been found secondarily in the skin.

Of 70 squamous carcinomas with metastases only 3 instances were not regional in their dissemination (Burke: AmJCanc 30 493 1937) Of 135 primary carcinomas of the lung 6% led to the production of skin lesions (Arkin and Wagner: J 106: 58 1936). The tracheal primary carcinoma rare itself, seems more likely than other lung cancers to invade the skin Keeney (BullJHH 61: 411 1937) reported such a case in an old man whose cutaneous nodules were first seen on the chest and scapulas, later over the whole trunk.

A remarkable hemorrhagic crusted copper-colored eruption in a newborn proved to be carcinoma metastatic from the thymus (Bedford: CanadMAJ 31 501 1930) Metastatic papular and vesicular lesions universally distributed in a newborn resulted from a thymic primary (Wasserman et al.: JPediat 14: 798 1939) Lesions resembling inflammatory ... affected the thighs in ovarian cancer (Urbach et al.: ADS 43 962, 1941) Nodular lesions of the scalp simulating turban tumor were prostatic in origin (Ronchese: ... 41: ... 1940) Subcutaneous nodules, usually on the same side as the affected bronchus, occur in pulmonary cancer (Charache: AmJCanad 37 431 1939) Secondary lesions in the skin of the toes were found in a woman with chorioepithelioma (Zoon: DWchs 10... 1936) Metastases appeared only in the skin subjected to irradiation in a patient with cancer of the pylorus treated with x ray therapy (Hebrehi: ZtschrKrebsfor 41 ...

Small nodules in the glans were secondary to adenocarcinoma of the rectum in the case of Stein and Hutsch (J 104: 1770, 193) The primary was ... in the case of M ... kson et al. (ADS 59: 50, 1949) which resembled ... chancre. Metastatic adenocarcinoma caused genital papules resembling moist ... syphilis in the patient of Winkel trut r (DWchs 111: 614 1940) ...

Transmission of maternal cancer to the fetus in utero has been known ... although it is rare ... melanoma (p. 1093)

Etiology of Metastasis.—Metastasis is rendered more probable by massage or manipulation as has been shown by the experiments of Tyzzer (J MedRes 28 309 1913) and Marsh (JCancRes 11 101 1927) using transplanted and spontaneous breast carcinomas in mice Schmidt (Die Verbreitungswege der Carcinome Jena, 1903) showed that intravenous injection of

an emulsion of cancer cells results in the successful implantation of a few of them in new locations. Saphir (SGO 63 775 1936) demonstrated tumor cells on the blade of a knife used to cut through a breast cancer thereby apparently explaining some of the instances of seeming transplantation of tumors in surgical scars, such as those reviewed by Lazarus (AnnSurg 107 278 1938) While Handley has championed the belief that the extension of carcinoma is mainly by actual continuity and has shown that the location of breast cancer metastases manifests a centrifugal tendency as the duration of the case increases, Long (AmJCanc 23 797 1935) was unable to find demonstrable continuity in a carcinoma of the wrist with axillary node involvement despite serial sectioning the lymph node lesions being therefore seemingly due to emboli.

EXPERIMENTAL INVESTIGATIONS OF METASTASIS.—There appeared to be no correlation between the size of the primary and the number of metastases (Zeidman: CancRes 9 629 1949) Transplantation of large fragments provoked more metastases than small fragments, and it seemed that the number of metastases was proportional to the number of viable tumor cell emboli released into the circulation, in the experiments of Zeidman et al. (CancRes 10: 357 1950) Hydrodynamic principles largely account for almost all phenomena of metastasis, believed Walther (Krebsmetastasen, Schwabe, 1948 560 pp.) Intravascular injections of cancer tissue suspensions were made in the study of the distribution of metastases by Coman et al. (CancRes 9 649 1949) When injected into the left side of the heart, they reached all organs and produced metastases in them. When injected into the femoral artery the leg muscles, ordinarily seldom affected, suffered massive instances. If an organ rarely supports metastases, the implication is that tumor emboli seldom reach it by way of the arteries. When tumor fragments were transplanted into various tissues, there appeared to be no difference in organ vulnerability (de Long and Coman CancRes 10 513, 1950); the scarcity of metastases in certain organs appeared to depend on factors other than the capacity for the organ to support tumor growth. Easily detached cancer cells, singly or in clusters, are actively ameboid, according to Coman (CancRes 13 397 1953) He pointed out that embolic cells may or may not be able to establish secondary growths in the sites where they arrive by way of the blood. Yet the duration of the primary tumor is known to bear a relation to the number of metastases, and mechanical factors affecting the frequency distribution of secondary tumors require elucidation before hypothetical "soil factors" are to be credited.

TEMPERATURE AND METASTASIS.—The relationship of body temperature with metastasis and its progress was interestingly brought out by Fay and Henny (SGO 66 512, 1938) Their investigations showed the relationship of skin temperature with segments of the body (dermatomeres) the gradients revealing the breast (5th dorsal) to be warm and the rest of the trunk cooler; the head and neck were warmest, the body 6.3 F lower than the mouth, and the acral regions (distal portions of the extremities) from 1 to 20° F lower in temperature than the mouth. Metastases were favored by warmth, they found. Local refrigeration relieved pain associated with a metastasis. Refrigeration resulted in diminution in size of metastatic lesions. In one case roentgen atrophy of the pituitary thyroid and ovarian glands caused a drop of 29% in the basal metabolic rate a corresponding fall of the skin temperature and the disappearance of widespread skin metastases.

Prognosis and Treatment.—The excision microscopic examination and recognition of metastatic lesions may occasionally first lead to diagnosis of the primary tumor Their prognostic import is obviously grave Death eventuates as a rule within 3 months of the appearance of dermal secondaries arising from the gut (Suzuki JCancRes 3 307 1917) Scalp metastases from a mammary cancer responded favorably to testosterone injections given by Cutler and Schlemenson (J 138 187 1948) Metastases in the skin are generally quite radiosensitive although under the circumstances treatment is usually neither requisite nor useful. Cancer recurring in a surgical scar however should be excised promptly (Meyer Gynéc 37: 263 1938)

See Lymphosarcoma, Melanoma, Sarcoma, Hemangiosarcoma Kaufmann-Wolf (AfDuS 114 769 1913) 65 cases of skin metastasis from internal organs, mainly stomach, bronchi, lungs Lee and Tannenbaum (SGO 39 580, 1924) 28 inflammatory carcinomas of the breast Connor (ADS 31 712, 1935) papules and plaques generalized, primary in bladder; Brown and Ormsby (ADS 34 1066, 1936) plaques, stomach primary; Dealy (AmJSurg 36 133, 1937) wenlike; T[illegible] (SurgClinNoAm 18 1309, 1938) secondary tumors in vagina and vulva; Schwartz (ADS 39 1026, 1939) hundreds in upper trunk and neck, stomach primary; Dörmgeler and de Castro (ArpathAnat 303 870, 1939) diffuse infiltration from hypernephroma; Kasten (JUrol 42 92, 1939) nodules in arm, scrotum, glans from hypernephroma; Bude (AfDuS 179 287 1939) review Stewart et al. (ADS 41: 645, 1940) extension from carcinoma arising in osteomyelitis; Kodl (AfDuS 181 37 1940) hypernephroma nodule in cheek; Camiel and Holber (SGO 72 635, 1941) carcinoma erysipeloides following mastectomy; Murrell and Pepple (ADS 57 930, 1948), cherry size, firm, blue nodules in young man's skin from testicular chorioma; Torrey (ADS 60: 1048, 1949) vegetative in neck from woman thymoma;

Rosebese (ADS 59: 229 1949) patchy alopecia of scalp from breast primary Layman and Becker (ADS 59: 626, 1949) massive secondary scalp meningioma. Harvey and Cochrane (ADS 62: 651, 1950) carcinoma en cuirasse stomach primary McDonald et al. (ADS 61 276, 1950) 13 cases of bladder primary; Ortega et al. (AnnWestMAS 5 401, 1951), metastasis of one neoplasm into another: melanoma of eye into renal carcinoma, bronchial carcinoma into adrenal adenoma, breast carcinoma into uterine fibroid, tongue carcinoma into leukemic neck node, review. Leavell and Tillotson (ADS 64, 774, 1951) cutaneous nodules, therapy Eversole (SouthMJ 45 28, 1952) in scar of bladder surgery, with intraepithelial growth Clements (J 150: 556 1952) 4 umbilical metastases Wartski (AustralJD 1 281, 1952) crusts and cicatricial alopecia, breast primary Howell and Riddell (J 154 12, 1954) source of scalp metastases; Rabson et al. (AmJClinPath 24 572, 1954) metastasis of cancer to cancer Schiff (AD 71, 466, 1955) 2 testicular tumors with skin metastases limited to the scalp Goldie et al. (PAACancRes 2 19 1956) cortisone given mice with cancer did not influence metastatic spread, but promoted growth of metastases; Schiebel et al. (J 157; 1488, 1955) metastases at umbilicus (q.v.)

SKIN MANIFESTATIONS ASSOCIATED WITH INTERNAL CANCER

Dermatologic manifestations distinct from metastatic phenomena are not infrequently associated with malignancy Most of such dermatoses on record have been atypical and did not fit any definite clinical entity wrote Gammel (ADS 66 494 1952) Eruptions resembling or suggesting the diagnosis of dermatitis herpetiformis have been the most frequent type. In reporting a bizarre eruption which he called erythema gyratum perstans (q.v.) associated with carcinoma of the breast and disappearing shortly after surgical removal of the cancer Gammel noted that the main types of skin manifestation associated with internal cancer are, as classified by Rothman (AfDuS 149 99 1925) (1) pruritus and a prurigo-like syndrome with hyperpigmentation (2) toxic bullous eruptions (3) metastatic cutaneous lesions and inflammatory lesions preceding metastases (4) acanthosis nigricans and similar proliferative changes and, Gammel added, (5) urticaria.

Explanations are hypothetical and concerned with the supposed absorption of, and allergic reaction to products of metabolism, degeneration or infection of tumor tissue. Cancer may cause various dermatological phenomena other than metastatic lesions by causing cachexia and malnutrition, which are followed by pigmentation (p 791) pruritus (p 823) or hypoproteinemia (p. 873) and by the dermatological consequences of these.

Widespread papular and erythematous, pruritic rashes and even exfoliative dermatitis were observed by Becker et al. (ADS 45 1069 1942) who reviewed the literature and presented patients with dermatoses associated with carcinomas of the pancreas and of the stomach.

Pachydermoperiostosis associated with, and possibly preceding the development of, cancer of the lung was described by Castex et al. (PrensaM Argent 36 3 1949) According to Andrews (Diseases of the Skin, Saunders, 1954, p 656) there occur thickening and accentuation of the folds of the skin of the forehead, upper eyelids, ears, lips, hands and fingers. In a case presented by Marmelzat (AD 72 90 1955) the chest x ray was negative and Becker recommended an abdominal exploration.

See Acanthosis nigricans, Lymphosarcomas; Erythema, symptomatic; Wiener (Skin Manifestations of Internal Disorders, Mosby 1947 p. 509)

DISEASES AFFECTING ESPECIALLY THE CUTANEOUS APPENDAGES

THE HAIR

Early chapters of this text provide descriptions of anatomy and embryology of the hair and there are paragraphs on the scalp and other hairy areas in the section on regional distribution of common dermatoses. In Dermatoses Due to Chemical Agents, contact dermatitis is discussed as it affects the scalp especially with regard to cosmetic and toilet articles. Dermatoses due to viruses wherein the scalp is often involved include varicella, herpes zoster and verruca. Dermatoses due to bacteria involving the scalp include infectious eczematoid dermatitis, acne miliaris necrotica, folliculitis and syphilis. Dermatoses due to fungi wherein the hair is affected include tinea capitis, kerion leptothrix, piedra and favus. Diseases due to animal parasites wherein the hair and scalp are concerned include onchocerciasis tick bite paralysis, pediculosis and phthiriasis. Dermatoses due to metabolic disorder wherein the hair is affected include eruptive xanthoma, seborrhea, various endocrinopathies such as pituitary basophilism with their cutaneous symptoms, avitaminosis and starvation syndromes. Dermatoses due to neural and psychiatric disorders affecting the hair include trichotillomania and neurotic excoriation. Pruritus of the scalp otherwise unexplained, is often due to hypoproteinemia. Dermatoses due to undetermined causes include many diseases with lesions commonly found in the scalp such as infantile eczema, atopic dermatitis, lichen chronicus simplex, arteritis of the temporal vessels, quinacrine lichen planus psoriasis, exfoliative dermatitis seborrheic dermatitis, discoid lupus erythematosus, dermatitis herpetiformis, scleroderma and morphea. Dermatoses due to malformation and neoplasia wherein the hair is concerned include keratosis pilaris, congenital ectodermal defect, congenital skin defect of the newborn nevus cell tumors, linear nevi, melanoma, neurofibromatosis and its variants, hemangioma, pilosebaceous adenomas, wens, sebaceous and dermoid cysts, cutaneous horn carcinoma, various sarcomas (especially the lymphosarcomas) and metastatic tumors in the skin.

The arrangement of material within this chapter takes the more or less orderly form of presenting congenital and acquired disorders of the hair, noninflammatory and inflammatory disorders; too much hair hirsutism, and too little, atrophy and the alopecias and disorders of color intrinsic and extrinsic. Parasitic diseases, as well as all other diseases named in the preceding paragraph have been discussed heretofore.

REFERENCES ON HAIR.—See Anatomy hair, Embryology, hair Physiology, chemical composition Tinea, trichomycosis, leptothrix, piedra, trichonodosis; Neuroses, trichotillomania. See Beigel (The Human Hair London, 1869) Jackson and McMurtry (Treatise on Diseases of the Hair Lea & Febiger, 1912); Danforth (ADS 11 494, 637 804 12 76, 195, 380, 520, 1925); Hubbard (A Treatise on Diseases of the Hair and Scalp, Lea & Febiger 1938); Cockayne (Inherited Abnormalities of the Skin and Its Appendages, Oxford U Press, 1933) Jalewsky (HandbHoG, Springer 1932 13 pt. 1, pp. 120-437), Sabouraud (Nouvelle Pratique Dermatologique, Masson, 1936, vol. 7 p. 125) alopecia, Hollander and Casselman (J 109 91, 1937) anatomy physiology and anthropology of hair on face, shaving technic Shellow (ADS 36 1224, 1937) proposed "trichomadesis"; Lochte (Atlas der Menschlichen und Tierischen Haare, Schops, 1938, 306 pp 590 illustr); Danforth (PhysiolRev 19 94 1939) Wigley (Practit 142 48, 1939) alopecias McCarthy (Diseases of the Hair Mosby, 1940) Ackermann (Dermatologica 81 310, 1940) review and bibliography on appendage diseases Okuda (abs ADS 43 567, 1941, RJD 53 92, 1941) transplantation of individual living hairs; Goodman (UCalRev 47 450 1943) permanent waving; Young and Rice (JLabClinM 29; 439, 1944) arsenic in hair medicolegal; Levin and Behrman (Your Hair and Its Care, Emerson, 1945) [illegible] (The Hair and Scalp A Clinical Study With a Chapter on Hirsuties, Wood, 1946, 304 pp) Pinkus (JID 9 91, 1947) life span studies on 12 hairs in nevus; Goldman and Mason (JID 11 323 1948) congenital and acquired defects of hair in children; Bouteiller et al. (Affections de la chevelure et du cuir chevelu, Masson, 1953) comprehensive and fine.

WOOLY HAIR

Wooly Hair occurred in 53 members and skipped 38 members of a family investigated by Mori (AItaldiAnat 22 123 1925) *the race was pure European.* A child with a similarly affected mother was seen by Gotthell (JCutD 37 489 1919)

Wooly Hair Nevus —Sharply demarcated patches of otherwise seemingly normal scalp produced kinky fine silky light-colored hair adjacent to the normal hair, which was long straight dark brown and solid in texture Seen by Wise (MJ&Rec 125 545 1925) in 2 girls each 5 years old, this was a congenital anomaly *Cases have been presented by Anderson (ADS 47 286, 1943)* Sweitzer (ADS 58 643 1948) and Hoffmann (Dermatologica 107 281 1953)

Acquired Progressive Kinking of the Scalp Hair —A remarkable case in which the scalp hair originally healthy straight and light brown in color became progressively wooly kinky and black was recorded by Wise and Sulzberger (ADS 25 99 1932) The patient was a Russian Jew 19 years old when this curious metamorphosis commenced. The hair of the left temporal region was first involved. Gradually the same changes took place on the right temporal area and were followed without intervals of interruption by similar alterations on both parietal and frontal areas. There were no other symptoms Biopsy showed no discernible alteration in follicular structure and the pathogenesis remains unexplained.



Fig 1301 —Acquired progressive kinking of the hair (Photograph of Drs Wise and Sulzberger from Behrman The Scalp in Health and Disease Mosby 195)

KNOTTING OF THE HAIR

Knotting of the hair is probably commonplace MacLeod (BJD 19 40 1907) recorded a case in a girl in which true knotting of scalp hair occurred and Kren (WienKlinWchn 1907 p 916) who carefully investigated the subject stated that true hair knotting is not unusual, for he found it in over 60% of a series of 54 women with various dermatoses. The nodular tangle is often in the form of a slipknot (Hess DWchn 85 1103 1925) as illustrated by MacLeod. Curliness of the hair predisposes to knotting the peculiar feel of which may bother the patient a great deal (Weiner ADS 58 278 1948) The disorder is to be distinguished from trichonodosis, which is synonymous with pseudoknotting and, correctly denominates pili torti (q v). A case was reported by Pratt (ADS 56 267 1947) and 1 associated with pediculosis by Scott (ADS 63 769 1951)

PLICA POLONICA

Plica (Polish plait Trichoma Weichselzopf) is a peculiar matted condition of the hair of the scalp, which occurs as a result of filth and neglect (Kaposi, in Hebra and Kaposi: Diseases of the Skin, London 1874, vol. 3 p. 75) The felted mass is usually moist as a result of eczematous oozing, and it generally contains large numbers of parasites, especially pediculi. While more common in Poland and Alaska than elsewhere the disease is occasionally observed in other co ntries. The pla t can perhaps be unravelled after preliminary sopping with petroleum it is better cut off It is readily prevented merely by washing and combing the hai

Plica neuropathica is a term applied to an "idiopathic matted or felted condition of the scalp hair Cases have been described by Stelwagon (AmJMedSci 104: 700 1892) LePage (BMJ 1: 160, 1854) and others. Th disorder usuall develops slowly It may involve the hair in only a small area. In Stelwagon's patient "The felting was limited to a dollar-sized area posteriorly just below the occipital protuberance, and had been a growth of years, forming a round matted, felted lock 4 feet long Pediculi or exudative disorders of the scalp are not present. It has been thought that twisting and tangling result from some peculiar shape of the affected hairs. It is possible that the cohesiveness of the hairs is due to a parasite simila to *Actinomyces som l easis* or *A. tenuis* productive of lepothrix (q.v.) which forms agglomerative secretions. Tangling was so extreme following the use of a det rgent shampoo in the case of Graham (AIM 67: 515 1953) that the hair had to be cut off

TWISTED HAIRS (PILI TORTI TRICHOKINESIS OF RIECKE)

Attention was called by Ronchese (ADS 26 98 1932) to a group of rare pilar anomalies characterized by twisting of the hairs, such as have been seen by Schütz (AfDuS 53 69 1900) Riecke (ZtrblHuG 5 437 1922) and Ormsby and Mitchell (ADS 10 393 1924 12 146 1925) This singular condition involved the whole scalp and the eyebrows of Ronchese s patient, a girl 7 years old, whose affection dated from birth, and of her young brother Twisting on the axis of the hair was in some sections in narrow and in others in larger twists. It was accompanied by dryness and brittleness of the shaft which resulted in alopecia over the occiput due to the habit of sleeping on the back. The relative baldness and the frizzy haired appearance were peculiar and the twisting which in many hairs was ropelike was readily observable and plainly different from the changes seen in monilethrix. Microscopically a slight twisting of the hair root was found, with atrophy especially in some places, of sebaceous glands and follicles. The hairs were weaker than normal in tensile strength and examination in polarized light revealed internal mal formation noted Hellier et al. (BJD 52 173 1940) The combination of kinky hair with blond complexion leads to trouble they thought. Usually only the scalp hair is affected although in 1 case of Galewsky (AfDuS 81 195 1906, trichonodosis 167 659 1932) the scalp beard, pubes, and even the lanugo hairs of the trunk were involved.

The anomaly occurred in 3 me in 1 family and in the 2 children of 1 of them reported Franchi (AItalD 10 267 1934) and was associated with k ratosis pilaris. A mother and he 5 children were affected, observed Touraine et al. (BsocfrançD 45: 441, 1938. A family showed partial alopecia, often in association with mental deficiency and the hairs resembled those of pili torti, in the report of Beare (BJD 64 366 195.)

Th pathogenesis is obscure but the dryness a d fragility seem due to th impaired secretion of sebum. Spiral hairs were present in 1 member of a family with mo ilethrix reported by Tomkinso (BMJ 1027 1936) Clarke and Glicksberg (ADS 43 836, 1941) reported the case f bov who was without hai until he was 5 years old, and they reviewed the literature In the case of Appel and Messina (NEngJM 226 912, 1942) a girl w th several sibs likewise affected, the condition was a form of ectodermal d splasia diff rent from Galewsky' disease As the patient grew olde the appearance of the hai pproached normal. The pplicat on f hydrous lanolin was helpful.

The condition, often hereditary was acquired in the patient of Suski d (ADS 56 540, 1947) following scarlatina; areas of the scalp showed patchy alopecia and supported hort, lusterless hair; generou doses of vitamin A were followed in a f w months by marked improvement. When the h ir regrew in a patch of alopecia whi h followed an insect bite, the regrowth was twisted, in the unusual case f Scott (BJD 62 472, 1950)





Fig 1802.—Knotted hairs (Dr F Ronchese.)
Fig 1803.—Trichostasis spinulosa. (Dr James H. Mitchell.)



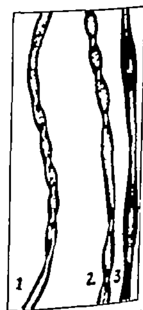


Fig 1804.—Twisted hair Alopecia, here, is due to fragility of hai (Ronchese: [Urol] Rev 37 549 1933.)

Fig. 1805.—Twisted hair and monilethrix 1 and 2 are twisted hairs, and 3 is moniliform. (Ronchese AD&S 26 98, 1932.)

TRICHOSTASIS SPINULOSA (PINSELHAAR, BUNDELHAAR LANUGO COMEDONES)

This peculiar disorder affects hair follicles of the shoulders, back and sides of the thorax (Galewsky AfDuS 106 214, 1911 138 451, 1922) the follicles contain blackish, elevated, horny spinous plugs, which fill the dilated orifices but can easily be removed These keratotic plugs contain bundles of lanugo hair which protrude beyond the *ostea* and can readily be palpated. The nape of the neck and the back are the common sites, but the peculiarity has been found in many regions (Corson ADS 38 363 1938) even on the nose (Fanburg ADS 27 274 1933) Suggesting the name pinselhaar (paint brush hair) Franke (DWehn 55 1269 1912) reported a case. Nobl (AfDuS 114 611, 1913) published an exhaustive study of 6 cases, and Caillag (AfDuS 117 3 1913) described the condition as lanugo-komedonen. The pathologic changes were exhaustively investigated by Hochstetter (DZtschr 20 316 1913) Mitchell (ADS 11 80 1925) gave a complete description. His first case the first recognized in America, like all others occurred in a man. The lesions, which at first appeared to be ordinary congenital, follicular keratoses, appeared to involve only *fairly well-defined areas on the dorsal surface of* the trunk and on close examination the involved follicles were found to be distended by funnel-shaped horny plugs which were readily removed by tweezers, leaving gaping orifices. The horny spicules were elevated above the level of the skin and could readily be palpated.

The condition was explained by Hochstetter as either of 2 possibilities (1) there is an abnormal congenital separation of the papilla of the follicle, such as normally occurs in the pig, or there are multiple papillae or (2) all of the hairs are produced by 1 papilla, but the hairs are not expressed from the papilla as they are formed, but remain in situ and form the brushlike bundle. Corson (1938) depicted plugs with delicate hairs wound around them. Burgess (ADS 25 40 1932) believed that the condition represents a development late in life of a congenital malformation of the follicles.

The deformity is a congenital one and treatment is only palliative or experimental. Recourse may be had to salicylated oils or ointments. One may imagine that estrogenic substances and efforts to secure endocrine balance would help

See Pandorpy (Dermatologica 79 144 1939) Decker (ADS 44 940, 1941) case Dowling (BJD 52 6, 1940) in fetus! Ladany (JID 23 33, 1954) 7 cases and review

GROUPED AND MULTIPLE HAIRS

Ordinarily 1 papilla produces 1 hair each being a single thread made up of concentric layers, never branching (Pinkus: JID 17 291, 1951) This is true of all hair not merely human. In trichostasis spinulosa compound follicles, sebaceous and dermoid cysts, and the disorder known as multiple hairs, it is possible for more than one hair to emerge from a common orifice.

Compound hairs, according to Loewenthal (JID 8 263 1947) implies the presence of more than 1 hair in 1 follicle. Twin hairs may spring from a papilla, join in the midportion of the follicle by merging of their cuticular cells and separate distally Grouped hairs signifies that 2 or more hairs emerge at such close proximity as to appear to be compound. Loewenthal stated that grouping and compounding of hairs may be found, if sought, in the majority of normal scalps, sometimes on the limbs and pubes, rarely in the beard. When folliculitis of the scalp occurred, excessive compounding of hairs was found but no increase in the normal proportion of grouped hairs.

A multiple hair was first described by Fleming (MonatshPrakD 2: 163, 1883) who discovered fortuitously a triplet hair in skin from the beard. Pinkus quoted also the finding by Giovannini of as many as 5 shafts surrounded by a common root sheath. Pinkus found as many as 7 which in an area of folliculitis

arose from a broad bulb reminiscent of a tulip bulb sheath containing several daughter bulbs. He proposed the name pili multigemini for the rare abnormality

DISTICHIASIS is a rare anomaly in which there is a double row of eyelashes on each lid, the posterior row replacing the meibomian glands. Szily (Klin MonatshAugenh 70 16 1923) gave a particularly thorough account with illustrations and wax reconstructions of the malformed structures. Cockayne (Inherited Anomalies, Oxford U Press, 1933 p 330) found records of 10 families in which the condition was inherited. The hairs of the accessory row are generally fine and blond it is their irritation of the cornea and conjunctiva which leads to their recognition.

Tristichiasis and tetrastichiasis have been described. The arrangement of the cilia may be considerably distorted.

INGROWING HAIR

It is common for one or several hairs of the beard to be set obliquely and to pierce and irritate the epidermis of the follicular walls (Pinkus ADS 47 782, 1943) They may not penetrate the corneum at all but grow beneath it. Such buried hairs cause small papules, which may suppurate These generally heal without scar Close shaving may predispose to their appearance but ingrowing hairs affect some individuals and are not found in others. Beards of men are the almost exclusive site

Tiny glassy asymptomatic papules containing fine black hairs are often seen on the legs and thighs. The hairs are doubled over and can readily be picked out as wiry loops constituting a disturbance which may be coincidental with, or actually a manifestation of keratosis pilaris (p 1052)

Papules containing ingrowing hairs should be pricked and the hair pulled out using clean hands and clean instruments and touching the wound afterward with a suitable antiseptic (QMN J 119 534 1942)

SCARRING PSEUDOFOLLICULITIS OF THE BEARD IN NEGROES

Folliculitis barbae traumatica described first by Dubreuilh (Presse méd 29 80 1922) was reviewed and investigated by Greenbaum (ADS 32 237 1935) and Pinkus (ADS 47 782 48 539 1943) In the Negro the curl of the hair results in its curving back into the skin after emergence from the follicle so that foreign body inflammation and eventual scarring develop The hairs come to lie in shallow grooves which persist as narrow cribriform scars when the hairs degenerate In treatment close frequent shaving has been advised on the other hand the argument is cogent that shaving should be avoided until the hair projects above the follicular orifice (Craig AD 71 11 1955) Temporary epilation with x rays may help The disorder is a recalcitrant one

SYCOSIS VULGARIS

Sycosis vulgaris is a form of chronic folliculitis. The disease is usually limited to the bearded region but the scalp may be involved by extension. The forearms and other hairy areas may rarely be affected. The essential lesion is a deeply seated or superficial acneic papule or pustule pierced by a hair After a lesion has persisted for several days its hair can be extracted easily usually along with the root sheath. In old pustular lesions, hairs are quite loose I would distinguish sycosis vulgaris from staphylococcic folliculitis a straightforward bacterial parasitism and from sycosiform tinea barbae (q v) which is straightforward fungus parasitism The bacterial disease often begins on the upper lip accompanying or following nasal infection, and from this locality it gradually spreads to other parts of the face Ultimately it may be associated with focal infection and malnutrition, as it may be it may involve not only the mustache and bearded regions, but also the eyebrows, lid margins, scalp axillae and pubes.

In sycosis vulgaris the inflammatory process is not so acute as in tinea barbae and boggy kerion like swellings are absent. The clinical picture remains that of pustular folliculitis. The eruption may be scattered or limited to 1 or 2 small areas, and such areas may expand and coalesce; or it may involve the entire bearded region. The course of the disease is tediously and





Fig. 1806.—Sycosis vulgaris. (Dr L. W Ketron.)
Fig. 1807.—Sycosis vulgaris, with discrete involvement.



Fig 1808.—Lupoid sycosis, having cicatricial alopecia and pustular lesions. (Dr. Marion Sulzberger from Behrman The Scalp in Health and Disease, Mosby 1952.)

rebelliously chronic While a few lesions may undergo spontaneous involution, new crops of papules are constantly springing up Blepharitis, typically marginal, along with more or less severe conjunctivitis is the usual accompaniment of severe sycosis. Destruction of hair and subsequent cicatrization are ordinarily comparatively slight, but alopecia may be extensive and scarring

a prominent feature. The patient is generally of poor economic and social condition in the United States, but in Great Britain those afflicted are often of well to-do classes.

'Lupoid sycosis,'' first described by Milton, was called Ulerythema sycosiforme by Unna. This begins in the outer portions of the bearded region and is characterized by gradual but progressive involvement of the hair follicles in this locality It is productive of hypertrophic and atrophic scarring and permanent alopecia. The patient of Wise (ADS 55 274, 1947) did not respond to penicillin.

Sycosis vulgaris has been attributed to strains of *Staphylococcus pyogenes*. Lowered resistance is a contributory factor whatever the term may mean perhaps avitaminosis is concerned. Pus, microorganisms and serum are found in the mouths of the follicles, the epithelial walls of which are edematous and permeated with leukocytes. As in all inflammatory processes, both the soil and the parasite must be taken into consideration. The problem seems to be one of altering the flora (Peck and Chargin ADS 29 456, 1934) perhaps this can be attacked by way of altering the soil, but staphylococcic vaccines are in general ineffectual. Staphylococci toxoid was tested by Forman (YBD 1937 p 386) in 21 cases, in which its use was followed by 2 fold to 4-fold increase in antitoxic titer of the blood, but not by benefit.

In treatment, it has been customary to supply the patient with a good pair of epilating forceps for the removal of diseased hairs. Each day the involved area may be poulticed with hot towels, carefully inspected, and all infected hairs epilated. This is followed by an antiseptic ointment such as 3% ammoniated mercury or 3% Vioform. Peck and Chargin (ADS 29 456, 1934) recommended

℞	Oxyquinoline sulfate	0.25
	Benzoyl peroxide	5.0
	Eucalyptol	0.5
	Oil of thyme	0.5
	Petrolatum	to 50.0

The addition of 3% sulfur and 0.5% chloramphenicol increases the efficacy of Vioform ointment. Vitamins, especially cod liver oil, riboflavin and nicotinic acid, were helpful, and alcohol must be interdicted according to Whitehead (PaMJ 42 1193 1939) Sulfonamides may be recommended, especially when they help to clear the urinary tract. Penicillin locally by compresses of 250 units per cc. (Alderson ADS 55 573 1947) or in an ointment vehicle (Russell BJD 59 294, 1947) was found likely to improve matters temporarily but is no longer used; tetracycline ointment is good. Tetracycline given by mouth is also beneficial in eliminating bacterial complication.

Roentgen therapy is valuable Shielding and technic must be meticulous to prevent ocular damage or unwanted hair loss. In dealing with refractory cases after conservative therapy has failed, the advisability of effecting permanent alopecia by x ray may be considered.

Focal infection must be attacked with energy Oral foci include dead teeth, dental root abscesses, pyorrhea, broken and decayed teeth, and infected tonsils. The prostate, bladder or urinary tract may harbor significant infection.

In recent years I have been successfully treating these cases, which are not frequent nowadays, the way I do acne (q v) with diet thyroid, estrogenic substances and x ray just as in the adolescent disease in the belief that sycosis vulgaris represents essentially follicular acne of a particular sort.

See Avit-Scott (BJD 45 199 1933), ichthyol Connor (PaMJ 31 1195, 1933) staph. coccus toxoid Tulipan (ADS 33 249 1936) brilliant green for blepharitis; Tzanck and Levi (BeocfrancD 45, 644 1938) Lugol iodine, Ingram (BJD 51: 59, 1939), foci of infect. [illegible] Abramowitz (ADS 37 1056, 1938), sulfonamide; Barrow et al. (BJD [illegible], 1946) [illegible] ointment; Fox (ADS 63 671 1948) no benefit with penicillin; Hobbs et al. (Lancet 2 [illegible] 1947) cultural studies suggesting reinfection from nasal discharge, benefit with peni[illegible] Johnson (ADS 58 741 1948) streptomycin ointment.

FOLLICULITIS CHELOIDALIS (DERMATITIS PAPILLARIS CAPILLITII)

Also known as Sycosis nuchae necrotisans (Ehrmann) and Sycosis fram boesiformis (Hebra) this exceedingly chronic inflammatory process involving the skin in the region of the nucha is characterized by folliculitis productive of nodular lesions of acneic, sycosiform and keloidal aspect The disease begins with the formation of a few or several rounded or acuminate pinhead size nodules in the region of the nucha at the border of the hair The little tumors are reddish in color and firm in consistency they tend sometimes to coalesce forming rough keloidal plaques. They range from pinhead to

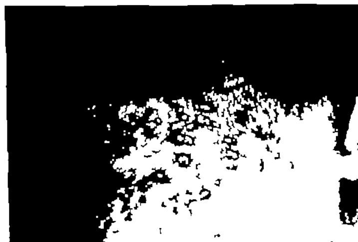


Fig 1809.—Folliculitis cheloidalis. (Dr Marion Sulzberger from Behrman The Scalp in Health and Disease, Mosby 1952)





Fig. 1810.—Acne cheloidalis (dermatitis papillaris capillitii)
Fig. 1811 —Perifolliculitis capitis abscedens et suffodiens

cherry size On section they are hard and gristly When punctured they bleed freely Pustules may spring up between the lesions, or the entire group may become undermined and boggy with circumscribed subcutaneous abscesses. Superficial ulceration is not rare Tufts of twisted, deformed and broken hairs project at many points through the nodules, along with comedones of bizarre shape.

The disease is usually confined to the nucha, but may extend upward on the occiput even to the vertex of the scalp The lesions give rise to symptoms mainly when they show acneic or furuncular inflammation. Ormsby (Diseases of the Skin, Lea & Febiger 1934 p. 1202) depicted a rare case involving the chin and quoted Samberger s involving the upper lip

Etiology and Pathology—The nature of the disease has not been generally agreed upon Older hypotheses concerned themselves mainly with micro-organisms and trauma, friction from the edge of the collar being thought significant in determining the localization. It is a disease almost exclusively of males Both acne vulgaris and hidradenitis axillaris bear marked resemblances I believe There is a wide range in the clinical expressions of the condition, some consisting of small *gristly* papules, others of boggy abscesses.

Treatment.—The lesions do not tend to regress spontaneously and they are rebellious to treatment. X ray therapy is helpful Filtered radiation should be used and treatment ought to be undertaken early before much scar formation has taken place *In late stages* it is generally necessary to push the radiation to the stage of permanent atrophy Excision of grossly deformed follicles cysts and nodules may be indicated. Plastic surgery may be required (Kanthak and Cullen SouthMJ 44 1154, 1951) One may lift up a flap containing the diseased skin and scrape it clean from underneath One may remove the tissue and substitute a full thickness graft My current treatment is as for acne (*q v*) of which I believe dermatitis papillaris capillitii to be 1 form. Estrogenic substances and tetracycline by mouth are often beneficial. In a patient seen by Sutton, Sr the disorder practically disappeared following tonsillectomy

See K pool (AfDuS 3 382, 1869), Hyde (JCutD 1 33 78, 1883), Vorner (AfDat 111 179 1912) Adamson (BJD 23 69 1914) benefit with x ray; Fox (AD# 65 112, 1H L nomenclature.

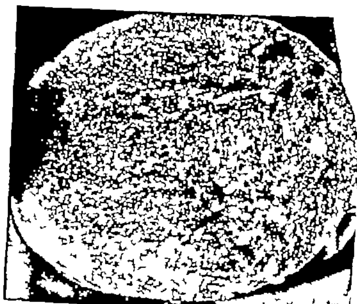


Fig 1812—Perifolliculitis capitis abscedens et suffodiens. (Dr Robert Barney from Mc Carthy Diseases of The Hair Mosby 1940)

PERIFOLLICULITIS ABSCEDENS ET SUFFODIENS

Dissecting Perifolliculitis of the Scalp a rare and sometimes severe affliction, is characterized by multiple abscesses of the scalp with undermining and granulomatous cellulitis. Many large and small nodules suppurate and intercommunicate by burrowing The lesions are hard to control by treatment and on healing leave irregular flat scarred bald spots, similar to those following folliculitis decalvans. The active nodules present the structure of granulomas with features suggestive of a tuberculous process. Cutaneous myiasis can produce a similar picture although of course larvae are present

H ffm (DZtsch 15 22, 1908) xhibited before th Berlin Derm tological Societ of 1907 a case of chr i flammatory disease of the scalp primarily perifollicular lei led

ing to suppuration and extensive undermining of the involved area, to which he gave the title used here. Similar cases were reported by Reute (DZtschr 20: 901 1913) Spitzer (DZtschr 10: 109, 1903) under the designation Dermatitis follicularis et perifollicularis conglobata, and Lang and Nobl (AfDuS 4 80, 1905) in Germany and by Wise and Parkhurst (ADS 4 750, 1921), Barney (ADS 44: 130, 1941) and others in America. Reute described the disorder as "a severe affection of the occipital portion of the scalp, which consists of many large and small nodules, which suppurate and intercommunicate by burrowing thereby undermining and excoriating a large part of the scalp The lesions are hard to control by treatment and on healing leave irregular flat, scarred, bald spots, similar to those following pseudopelade. Reute and also Wise and Parkhurst found that the active nodules presented the structure of tuberculoid granulomas. Barney believed the disease closely related to acne conglobata and obtained an eventual cure with sulfonamide which helped the patient of Costello (ADS 49: 154, 1944) Roop (ADS 3_ 819 1935) presented a case, a Negro 28 years old, who had syphilis; Weldman thought it an example of exceptionally extensive sycosis. The 5 patients of Aabeck (DWchn 105: 1606 1937) all of whom were by occupation "exposed to atmospheric influence, were unresponsive to therapeutic effort until the nodules were excised, after which the wounds promptly healed. Fever therapy and x ray epilation have been recommended (Cannon: ADS 49: 67 1944)

I agree with O'Leary's views [quoted by Brunsting (ADS 44: 131 1941) and attributed to the latter in a discussion of the case associated with hidradenitis of the crotch and axillae of Owens et al. (ADS 48: 226, 1943)] that the process is an acneiform affection. A Negress (ADS 40 144 1939) also had hidradenitis in axillary and pubic regions, and so also did the patient of Machacek (ADS 46: 897 1942), although she was an atypical example of the disease. The Negro case Machacek (ADS 5 : *1_, 1945) presented was typical, and the lesions of forearms, thighs, legs, buttocks and pubes resembled those of acne conglobata (p. 678)

I treat my cases, rare as they are with low fat diet thyroid and estrogen, tetracycline x ray therapy plastic surgery and elimination of focal infection Penicillin intramuscularly helped the patient of Cornbleet and Kagen (ADS 53 543 1946)



Fig. 1313 —Perforating folliculitis.

FOLLICULITIS NARIUM PERFORANS

Perforating Folliculitis of the Nose is characterized by a follicular abscess of a hair within the nostril which perforates the skin externally The bulbous base of the vibrissa presents within a small pustule on the external surface of the nose. Following extraction of this hair such lesions promptly heal. Culver (ADS 15 16 1927) originally reported 3 cases. Palmer (ADS 38 429 1938) recorded 1. The affection is manifested by the occurrence of a small pustule on the side of the tip of the nose Despite incision and drainage the lesion is persistent Ultimately a crust forms, and when this is forcibly removed, the bulbous end of the affected vibrissa is found to be attached to the inspissated mass. The affected hairs are typical of those occurring inside the nostril and are never curled or corkscrewlike as in pili incarnati. The condition is apparently rare It could easily go unrecognized. A dermoid sinus tract of the dorsum of the nose (*q v*) might be mistaken for perforating folliculitis this may have been true of the case presented by Rein (ADS 44 969 1941 45 235 194)

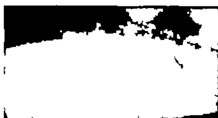


Fig 1814.—Hypertrichosis.





Fig 1815.—Hirsutism associated with masculinizing ovarian blastoma. (Rottino and McGrath Arch Int M 63 686, 1939.)

Fig 1816.—Masculinovoblastoma, skin changes (Drs. Rottino and McGrath.)

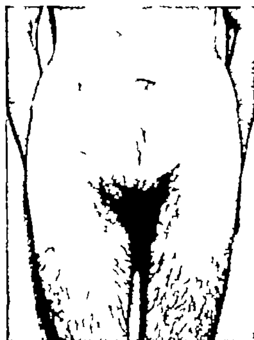




Fig 1817.—Hirsutism from ovarian arrhenoblastoma; see Fig. 1818.

Fig 1818.—Disappearance of excess hair after removal of ovarian tumor from patient shown in Fig 1817 (Maxwell, from Crossen Diseases of Women, Mosby 1935.)

HYPERTRICHOSIS (HIRSUTIES)

Hypertrichosis excessive or abnormal hairiness from any cause, may be congenital or acquired. It may be of limited or universal distribution. Localized heavy growth, particularly in pigmented areas on the lower trunk buttocks and thighs, is not extremely rare and is described with hairy nevi (p 1066), see also p 1074

Hypertrichosis Lanuginosa, the universal, "dog faced" type, is extremely rare. Hirsutism may be present at birth or may develop during childhood. In a case seen by Sutton, Sr., the growth first became marked during the patient's sixth year The hairs were soft, downy and of a light yellow color The entire surface, except the palms and soles was affected, particularly the face and forearms. On the forearms the hairs were closely set, and averaged 5 cm. or more in length. There was no hereditary correlation. Weber (Brit JChildDis 14 272 1917) described a similar case Cockayne (Inherited Abnormalities, Oxford U Press, 1933 p 245) described the familial cases as follows



Fig 1819—Remarkable localized hirsutism in a boy present since birth.

"As a rule the ears are hairy at birth, but the general hirsuties does not become noticeable until the child is between 2 and 7 years of age. The hair continues to grow in length and thickness until soon the face, trunk and limbs, with the exception of the palms, soles and prepuce are covered with long, silky hair of a silvery grey or pale yellowish color On both sides of the ears, on the cheeks and on the forehead it may attain a length of 8 to 10 inches, on the nose and chin it is about 4 inches long, and on the trunk and limbs the length varies from 4 to 8 inches according to the site. The axillary and pubic hair is lanugo. The features appear to be quite shapely, and the skin is unusually clear but the hair gives these people an appearance not unlike that of a Skye terrier There is considerable variation in dentition from almost complete absence to a lack of 2 or 3 teeth. Details of the dentition of several cases are given by Danforth (1925)"

Unusual hypertrichosis in a child 2 years old was reported by Aquirra (BsocPéd 25 297 1927) and in a boy 12 years old by Eschbach (BsocPéd 25 307 1927) Hypertrichosis of the ears appeared as an anomaly of startling appearance in the males of a family reported by Tommasi (quoted by Cockayne) Hypertrichosis of the eyebrows and eyelashes was a striking feature of a man and his 2 daughters reported by Marquez (quoted by Cockayne) This disorder is common and occasionally appears as a familial characteristic in the males; it may be extreme as in the family reported by Monteiro (quoted by Cockayne)

Hypertrichosis of Malnutrition affects especially the legs of boys and girls and diminishes after the persons have been properly fed (Castellani JTropM 41 400 1938) Hypertrichosis in patients with tuberculous meningitis might be of this sort according to Centrangolo (abs J 153 1219 1953) it is more frequent in children, appears during the first 3 months on antibiotic therapy lasts for from 3 months to a year and disappears when clinical improvement is attained.

Acquired Hypertrichosis is a comparatively common disorder The areas commonly affected are the cheeks chin and upper lip and occasionally the forearms and legs. Such hypertrichosis is usually partial, although a few universal examples have been recorded by Zarubin (JCutD 15 14, 1897) and others. The woman reported by Lyell and Whittle (BJD 63 411 1951), resembling the patient of Ormsby (ADS 21 663 1930) developed hypertrichosis lanuginosa a few months after undergoing cystectomy for bladder cancer

There are 2 types of acquired hirsutism in women, Marton (MRec 143 150 1936) wrote the type affecting the corners of the mouth and the edge of the chin, not associated with endocrine disturbance in his opinion and the type affecting the sides of the face and the lower half of the body generally accompanied by irregular menses, perhaps even sterility

Localized hypertrichosis may appear at sites where idiots suck and bite their skin (Rassmann and Butterworth ADS 63 453 193) The possibility of the medicolegal determination of sex by hair (Kosslakoff's reaction") has received consideration interesting observations were published by Kosslakoff (VrachDelo 1 873, 1929) and Serebriaaikoff (SudelMedEkspert 10 19 1928)

Excessive growth on limbs following nerve injury or beneath a plaster cast probably result from diminution in the frictional loss to which the hair is normally subjected (see J 114 973 1940) Long Hair Chief of the Crow Indians, had scalp hair 10 feet long (Corson ADS 56 443 194)

Apparent hair growth after death is probably nothing more than increment in its projection as the tissues shrink (QMN: J 116: 964 1941)

TRICHIASIS.—Occasionally hairs deviate from their normal course and in certain localities, as at the margins of the lid , the deformity may give rise to more or less discomfort or even injury The annoying hairs should be removed by electrolysis. Compare Distichiasis.

SCHRIDDE'S CANCER HAIR may be present both in persons with cancer and in those without it (Frick and Meduna: KlinWehr 49: 76 1936) The sign consist in a number of deep black coarse, d ll hairs on the frontal a d temporal margi of the scalp. It is an observation that the large majority of persons who have squamous carcinoma of the skin have a reddish tint in their hair which may be either blond or brunet.

Etiology—Why hair grows is a problem in embryology a field in which problems are tantalizing but answers are elusive As a chemical organizer can in fact promote the elaboration of an eye a limb or another course of differentiation, so it is a reasonable hypothesis, chemical substances in the skin humoral or sessile promote the organization of a hair from primitive epithelial and mesodermal elements.

Under some circumstances a lanugo hair may develop into a large stiff bristly one Whether shaving trauma, erythema inunctions or other local phenomena are pertinent to the change is uncertain. Shaving probably encourages the growth (Hu and Frazier AnatRec 77 155 1940) Trotter (AJPA 7 93 1923) found that the rate of hair growth is little affected by sunshine greases or shaving but that it is functionally related to the cross sectional area It is a widely accepted opinion that shaving encourages the growth but the hair being as lifeless beyond its follicle at the place where it is cut as is the fingernail where it is trimmed one does not know the mechanism which might explain this dubious belief. It seems to me that the beard grows faster in the summertime than in winter months when the face is cool.

Hirsuties in women may be classed in 3 categories (Cr pell et al CP 11 82, 1955) (1) hirsuties with virilism (2) hirsuties with nonvirilizing endocrinopathies and (3) hirsutism without recognizable endocrine disorder A strong family history of hypertrichosis suggests that no endocrine basis will be discoverable In women with endocrine disorders, one may find changes in

the menstrual pattern, increased growth rate of the excessive hair changes in hair texture from fine to coarse, changes in distribution of hair from feminine to masculine and evidences of masculinization with deepening of the voice or hoarseness diminution in size of the breasts, enlargement of the clitoris, increase in the heaviness of the musculature, development of acne on the face and trunk, and the appearance of frontal baldness.

VARIOUS ENDOCRINE IMBALANCES greatly influence the growth and distribution of the hair They do so I suppose in the same manner in which chemical substances influence organogenesis. The adrenal gland, itself greatly influenced by the thyroid and the pituitary seems particularly involved, all 3 of these glands influence the gonads. Knowledge of hormones concerned with growth of hair is still so sketchy that therapy based on it is seldom of practical

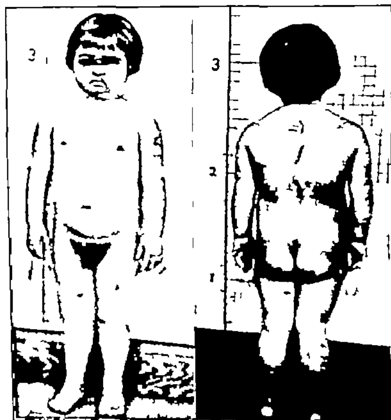


Fig. 1626.—Hirsuties and precocious puberty in a girl 4¼ years old who had a tumor of the adrenal cortex. (Dr Hector Mortimer from Meakins Practice of Medicine, Mosby)

use Sexual function is related to hair growth (MacKenna Diseases of the Skin, 1937 Wood, p 470) I have seen excess of hair of the upper lip and chin disappear in women following marriage I have seen it make its appearance after divorce. I have seen hirsuties follow thyroidectomy It is common for hair of the face to grow and darken during pregnancy Long coarse hairs of the ears in Caucasian males indicate that androgenic hormone is or has been adequately supplied (Hamilton Trans. Soc. Inv D., 1947) Sex *hormone* influence on hair growth was studied by Hooker and Pfeiffer (Endocr 32 69, 1943) principal effects were on the sebaceous glands, estrogen reducing, and androgen augmenting, their size and activity Estrogen was of temporary benefit in hirsuties in women in experiments of Dorff (AnnIntM 13 2112, 1940) though its topical application was a failure according to Whitaker et al (JID 9:49 1947)

Large doses of estrogen helped a girl with hirsuties associated with simple hyperplasia of the adrenal cortex, according to Leyton (MPract 221 44 1949). Mild hirsuties and anovulatory menstruation were frequent concomitants in sterility cases studied by Wong et al (AmJObGyn 60 790 1950).

Hypothyroidism is an unusual cause of hirsutism in children. The excessive growth on the back, shoulders, outer aspects of the arms and legs and, to a lesser degree, the sides of the face almost completely disappeared in the 4 cases treated with thyroid by Perloff (J 157 651 1955).

ADRENAL CORTICAL, PITUITARY AND OTHER TUMORS are capable of inducing masculinization and hair growth; see Cushing's syndrome and also its symptoms in connection with striae distensae and purpura.

The syndrome includes obesity of rapid onset, hirsuties, amenorrhea, hypertrophy of the clitoris, osteoporosis and hypertension (Freyberg et al.: AIntM 58: 187 1936; Cahill PaMJ 4 : 633 1944). The masculinization effected by a tumor varies with the age and sex of the patient, and one must be alert to the serious significance of the appearance of pubic hair and enlargement of the clitoris in a girl of tender years (Reilly et al. Endocr 24: 91 1939). Arrhenoblastomas and hypernephroid tumors (luteoma) are ovarian tumors causing masculinization which will dissipate when the cause is removed (Rottino and McGrath AIntM 63: 686 1939). A glioma of the left temporal lobe caused hirsuties in a patient of Markoff (SchweizMWchr 69 57 1939). An adrenal tumor within the ovary was masculinizing in the patient of Mortell (JNatCancInst 9 77 1949).

Virilism due to adrenal hyperplasia in 14 cases of Jailer et al. (J 150 575 1952) was treated with cortisone and there occurred a dramatic fall of total 17 ketosteroid values and abeyance of masculinity in the females. The removal of adrenal gland substance in patients with Cushing's syndrome who suffer from hyperadrenocorticism and excess production of 11-oxysteroids, will, if adequately done, be followed by return of the skin to normal color and texture and disappearance of hirsutism, stated Poutasse and Higgin (JUrol 70 129 1953).

Of 30 patients with hirsutism meticulously studied, 10 showed Cushing's syndrome and 9 had masculinizing ovarian tumors, reported Callaway et al. (ADS 60: 529 1949). If the hirsute woman has menses of normal duration, no symptom of virilization, normal temperature graphs and normal endometrial biopsy indicative of normal ovulation, it is most unlikely that endocrine disease exists, they stated. Amenorrhea and hirsutism in a grave prognosis, and diminishing menses, development of obesity, appearance of masculinization and alterations of psychosexual and libidinal physiology are indications that careful study is necessary. In essential hirsutism, Callaway et al. discovered no evidence of ovarian failure, no alteration of 17 ketosteroid excretion, and no cause that they could assign; and they secured no benefit from estrogenic therapy in such cases.

Treatment.—Indications suggesting the need for careful medical and gynecologic evaluation were noted in the paragraph on etiology. When the problem is simply that of removing excess hairs, one may assume that they are permanent unless their roots are destroyed.

Temporary relief can be obtained by shaving, which is more or less abhorrent to women, although some of them have no alternative, or by the use of chemical depilatories, the active ingredients of which include barium sulfide, calcium sulfide, strontium sulfide and calcium thiosulfate; a mixture of calcium and sodium thiosulfate may be employed.

A good formula is that of Duhring: take barium sulfide 2 to 4 parts with zinc oxide and starch in equal parts to make 1 ounce; add water to make a paste, spread thick onto the affected area, allow to remain for a few minutes until the offending filaments are dissolved, then remove, cleanse and apply cold cream. Depilatory methods have been given in answer to numerous inquiries put to the J.A.M.A.; see QMN (J 112 2348 1939 1[illegible] 1942 137 1568 1948 139 193 1949 151 166 1953).

Gentle rubbing with pumice stone has been found helpful. The frequent application of 20-volume hydrogen peroxide bleaches the offending hairs and reduces their visibility. All oil should first be removed with soap, ammonia water and alcohol, and the agent then applied.

ELECTROLYSIS is the safest and best means for destroying hair follicles. A direct current of from 1 to 3 milliamperes is used. The slender, specially designed needle with a bulbous tip is attached to the negative pole. A damp sponge is attached to the positive pole. After the operator gently inserts the needle along the hair shaft to the depth of the follicle (a dainty and tedious

task) the patient closes the circuit by touching the sponge with the finger In from 10 to 20 seconds bubbles appear at the orifice of the follicle, the patient is told to break the circuit, the needle is extracted and the hair if sufficiently damaged is readily pulled out. With clean skin and clean needle, infections do not occur Adjacent hairs are not attacked at one sitting for fear of scarring From 10 to 50% of the hairs so removed recur Single-needle technic is best. A multiple-electrode technic was described by Marton (APhysTher 21 678 1940)

ELECTROCOAGULATION by diathermy described by Memmesheimer (MKlin 1937 p 1133) and utilized by many workers, is not the method for the uninitiated. The time interval distinguishing destruction of follicle from destruction of skin is measured in small fractions of a second. The monopolar high frequency technic is fast (Karp ADS 43: 85 1941) but difficult of application and likely to scar (Ellis ADS 56 291 1947) Various instruments have been devised and described.

See Hand (ADS 48: 1094, 1943); Rosenberg and Smith (APhysTher 24: 277 1943), diathermy type; Davis and Noojin (SouthMJ 45 839 1952) selenium rectifier direct current device Niedelman (JClinEndocrin 13 451, 1953) high-frequency device with polyethylene tubing on needles to control depth.

ROENTGEN THERAPY depilates by producing follicular atrophy *The dose which depilates permanently produces permanent cutaneous damage.* While the agent can be used wisely and helpfully in hairy nevi, perhaps, its dangers and damaging effects were graphically described by Capollaro and Finborn (J 133: 349 1947) and by Cleveland (CanadMAJ 60: 3 4 1948) Cole (J 84: 865 1925) condemned the method roundly; its use for the treatment of hirsuties is malpractice. See Robinson (SouthMJ 40 619 1947)

The medical accomplishment in removing bristles from a woman's face when it can be done in a case not too extensively involved is well worth while and is appreciated. It is a job usually taught and assigned to an office assistant, but represents a service not to be underestimated and not to be allowed, in view of the skill required, to slip from the control of doctors of medicine

Many a girl, unduly disturbed by hairiness which is not outside the range of normal variability may best be talked out of fretting if possible and advised to adapt herself psychologically

Cortisone 25 mg b.i.d., was given to a number of hirsute women by Greenblatt (AmJObGyn 66 700 1953) with improvement in some of them. Those who improved on cortisone were the ones with virilizing adrenal hyperplasia in the experience of Segaloff et al (J 157 1470 1955)

See Gould and Pyle (Anomalies and Curiosities of Medicine, London, 1898, p. 228) Jo-Jo, the dog-faced man, etc Williams (AmJDermat 9: 176, 1905), treatment of hirsuties Knowles (PaHJ 24 401 1920-1921) hirsuties in childhood; Toomey (UOutRev 28 677 1932) electrolysis; Niemoeller (Superfluous Hair and Its Removal, New York, 1938) Lerner (MRec 151 193 1940), electrolysis; Monroe (J 117: 1928, 1941) curious lines barriness followed phlebitic vein; Grollman and Rousseau (J 126 212, 1944), hirsuties in 12 of 42 cases of hyperostosis frontalis interna; Pittesky and Last (Sci 108 657, 1948) depilatory for laboratory animals yellow barium sulfide 3 parts, commercial detergent 1 part, cream with 10% glycerol in water, wet skin, apply, remove hair rinse well, Dockeray (Pract 161 59 1948) Home causes of hirsutism; Whitaker and Baker (Sci 108: 207 1948) inhibition of hair growth by certain adrenal cortex compounds; Grant et al. (ADS 61: 717 1950) no influence of adrenal cortex extract topically Broster (BMJ 1 1171, 1950) hirsutism cases, anomalous types Kramer and Friederich (DWchn 133 263, 1951) nonirritating strontium sulfide formula; Hoomay and Higgins (PSEBMC 26: 321, 1951) hair regrowth in mice, effects of hormones and gonadectomy Friederich (ZschrHaut 12 176, 1952) strontium damages intrafollicular segment of hair, thioglycol cream does not affect this portion of the shaft; Albeaux Fernet et al (Hirsutism, Masson, 1954) exhaustive investigation of 30 patients exemplifying simple hypertrichosis, hypertrichotic virilism, and Cushing syndrome finding that ketosteroid excretion in excess of 50 mg. per day suggests tumor Goldzieher and Davidson (ObGyn 4: 342, 1954) masculinizing blastoma.

ATROPHY OF THE HAIR

This may be either symptomatic or idiopathic. Symptomatic atrophy is generally due to chronic debilitating disorders, such as cancer tuberculosis, diabetes or malnutrition, and it may occur as a result of a local disorder such as tinea or seborrheic dermatitis. It is characterized by dryness, splitting and curling of the affected shafts, with loss of flexibility Healthy growth of hair is conditioned upon the health of the body as a whole If the hair does not thrive the medical effort to correct it lies in correcting the economy of the individual, seeing to it that adequate rest relaxation and nutrition are ob-

tained, and endeavoring to adjust endocrine balance and to remedy anemia and iron deficiency if they exist. Diffuse hair loss in women is concerned usually with a need for iron. Not only standard blood tests but also the mean corpuscular hemoglobin concentration and the total serum protein are examinations worth making. Examination of the nails of a patient with complaints regarding the hair may be revealing: thin fragile nails with longitudinal striae strongly suggest the need for iron and liver concentrates. Sometimes hypoproteinemia is causative. A permanent wave does not take well in a woman oversupplied with thyroid, whether it comes from her own gland or from pills. Hair which is dry and breaks off easily is more likely to respond to estrogen than to vitamin A.

Idiopathic Atrophy of the Hair is a manifestation of congenital ectodermal defect (q.v.). Several varieties are described.

FRAGILITAS CRINIUM may be manifested by splitting or fragility of the shaft. Excessive washing, low humidity, hypoendocrine states and dietary deficiency are factors likely to be concerned. The patient complains that the hair is abnormal to the touch and seems to be parasitized by creatures she wishes to pick off or to brush out, and brushing the hair actually results in further splitting of its feathered ends. The scalp should be kept clean, and an occasional coat of an oily dressing may be applied, such as a scented mixture of petrolatum and hydrous lanolin. In splitting of the distal extremities of the shaft, clipping off the split ends may be desirable. Singeing is inconsequential, being neither helpful nor harmful. After the shaft has been pushed beyond the follicle its biologic structure has been determined insofar as it is of medical importance.



Fig. 1321.—Trichorrhexis nodosa. (Dr. Fred Weidman.)

TRICHORRHEXIS NODOSA (TRICHOCLASIS; CLASTOTHRIX; NODOSITAS CRINIUM) first described probably by Beigel (DenkschrWienAkadWiss 1: 61, 1855) is a peculiar nodose condition of the hair characterized by longitudinal splitting at intervals along the shaft, the formation resembling 2 small, round brushes pressed end to end. Complete or incomplete transverse fracture of the shaft may result. Several nodes may develop in a single filament. In men the mustache and the beard are the most frequent seat of the condition (Hodara, MonatshPraktD 19: 173, 1894), and in women the hairs of the scalp and of the labia majora (Raymond: AnndeD [illegible]: 568, 1891). It has been observed in the bristles of [illegible] having brushes. The condition may be circumscribed, affecting only a few hairs, or those of a single plaque, or perhaps the hairs of several isolated areas; or it may be disseminated, affecting the hair universally or all the hairs of a region (Touraine and Clerfeuille [illegible] BSocfrancD 1939 p. 636). The hair of the pubes and axillae occasionally [illegible]. The nodes are grayish in color and minute in size and their presence can ordinarily be detected only by careful search. The disease gives rise to little actual hair loss.

"Trichorrhexis is both a normal and a pathological process," according to Heidingsfeld (JCutD 23: 40, 1903). "It is universally present in long uncut hair as a normal condition and is probably nature's method of physiologically arresting and stunting an otherwise unlimited and eventually cumbersome overgrowth of hair. When present to excess in a predisposed individual, it becomes a pathological process and abnormally [illegible] the growth of the hair; the nodes are more prominent [illegible] normal hair [illegible] multiple, separated from each other by uniform intervals of normal [illegible]. Its etiology has been variously attributed to trophic, parasitic and mechanical influences. Mechanical causation is improbable on purely clinical grounds and is incapable of artificial demonstration. The condition in brushes can likewise not be attributed to [illegible] mechanical causes. A parasitic causation is not commensurate with the evidence adduced from clinical studies and bacteriological investigations. The most rational explanation of its etiology rests on trophic influences, emanating from the metabolism at large and permeating the hair to its ultimate extent."



Fig 1822.—Monilethrix (Mackee and Rosen JCutD 34 444, 1926.)

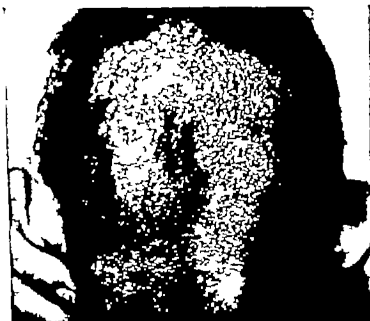


Fig. 1823.—Monilethrix A boy 11 years old The extreme alopecia and follicular hyperkeratosis are characteristic. (Dr Norman Tobias, from McCarthy: Diseases of the Hair Mosby 1940.)

If a hair consists of cells improperly maturated through nutritional influences, an abrupt angulation of the cylindric shaft by mechanical influences, postulated by Wolfberg (DMedWchn 10: 490 1884) does in fact occasion a nodose splintered fracture.

The disorder is persistent and rebellious to treatment. Epilation or frequent shaving may do good. I have not seen a case in years, but would try nutritional and endocrine therapy. Familial incidence, as described by Touraine and Solente (BsocfranD 44 1011, 1937) does not necessarily imply hereditary causation.

TRICHOPTILOSIS is longitudinal, featherlike splitting of the hair shaft into long fibrils. It results from brushing hair which is abnormally fragile. The similarity to trichorrhexis suggests that iron, estrogen and perhaps cortisone would be helpful.



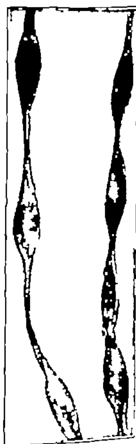


Fig 1824—Monilethrix. (MacKee and Rosen JCutD 34 444, 1916.)
Fig 1825.—Monilethrix. (Dr J F Payne)

MONILETHRIX (BEADED HAIR) is an anomaly usually congenital and frequently hereditary which is characterized by fusiform swellings separated by atrophic constrictions so that the affected filaments present a beaded appearance. The shafts are fragile and break readily at the internodal constrictions so that extensive alopecia is common. Keratosis pilaris is often present and leukonychia was concomitant in the case of Kislicenko (DWchn 108 516, 1939). The nodular sections contain excessive amounts of pigment, the constricted portions little. The entire shaft is generally affected. The disease is usually confined to the hairs of the scalp (MacKee and Rosen JCutD 34 444 506 1916) although Ruggles (JCutD 18 500 1900) reported involvement of the legs.

The disease tends to disappear in the course of time according to Tomkinson (BMJ 1: 526 1935 * 1077 1936) who reported cases in a girl, her mother and her brothers, and also noted its occurrence in 7 of 8 persons in a different family. The 5 cases of Tobias (ADS 7: 655 1923) were familial. Re n (BJD 46 168 1934) reported 8 cases in 4 generations. Franchi (AItalD 10: 767, 1934) saw it in 3 m les f f mil cons ting of 7 males and 2 females. It w s a domi ant character in 5 generation of the f mily of

Gottlieb (Hospitalstid 79: 751, 1936) and 3 cases were seen by Larsen (Hospitalstid 79: 129, 1936) in a family in which the condition was said to have occurred for centuries, so that he considered it "a hereditary trophoneurosis. Appel and Messina (NEngJM 226: 912, 1942) described an affected sibship, whose disorder they thought to represent an ectodermal dysplasia. The boy of Clarke and Glicksberg (ADS 43: 836, 1941) lacked hair until age 5. Weber and Harthausen (BJD 39: 62, 1927) reported an interesting example in a boy 3 years old.

Pathologically the epidermis between the hairs was thinner than normal, and in 1 follicle the mouth was almost blocked by a firm, dense, hyperkeratotic mass, noted Gilchrist (JCutD 16 157 1898). The nodes and constrictures could be traced down to the deepest fourth of the intrafollicular portion and there were corresponding narrowings in the lumen of the follicle. In the vicinity of the follicles the capillaries exhibited perivascular inflammatory changes. The hair papillae arrectores pilorum and coil glands were apparently normal. Bacteriologic examinations have proved negative. MacKee and Rosen (1916) in their exhaustive study of 7 cases, concluded that it is due to a congenital defect and is associated with keratosis pilaris, an affection considered by many as being closely related to ichthyosis.

The disorder is not readily amenable to treatment. Gilchrist's patient recovered spontaneously. Keratolytics, particularly preparations containing salicylic acid, and stimulants as well as massage may be tried. Van Leeuwen (ActaD-V 9 303 1928) secured an apparently normal regrowth of hair following epilation. X rays or thallium may be used for the purpose. Vitamin A may help. Attention should be given to all aspects of nutritional and endocrine balance. The fault lies in abnormal function of the hair papillae, in the opinion of Martin-Scott (BJD 62 35 1950).

ALOPECIA (TRICHOMADESIS)

Alopecia (Baldness) may be due to any of a number of causes. It may be partial or complete. It may be patchy or universal. It may be diffuse affecting only some hairs of the region, or complete affecting all in that place. Congenital and acquired types are recognized.

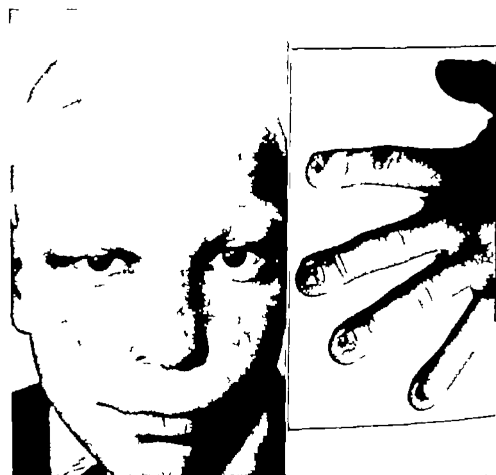
Congenital Hypotrichosis.—Partial or even complete deficiency or absence of hair may be a manifestation of congenital ectodermal defect (q v). Atrichosis congenitalis (alopecia adnata), the congenital absence of hair, is not unheard of. Sobajima (ZntralblHuG 29 445 1929) reported a family in which 29 males manifested a sex linked recessive form of alopecia congenita, and among them the hair was either absent at birth or fell out between the first and third years of age. According to Cockayne (Inherited Abnormalities Oxford U Press, 1933 pp 225 229) the isolated and familial cases of congenital alopecia are alike in exhibiting normal nails and well developed sweat glands and arrectores pilorum, but they differ in details. A boy and 3 girls of related parents were totally bald but were without other ectodermal defects, as reported by Gillespie (AmJDisChild 53 132, 1937). Cases of recessive congenital total alopecia were reported by Lundback (Acta D V 25 189 1944). The disease is known to occur in horses, cattle, goats, rabbits, rats and mice (Schede AfKlinChir 14 158 1872) and the absence of feathers from various fowls has also been noted. Incomplete follicles can be found microscopically in all these conditions. When hairy skin was transplanted to bald areas of rats affected with hereditary hypotrichosis, it took and grew in the experiments of Roberts et al. (JID 3 1 1940).

The association of hypotrichosis with Friedreich's ataxia, with webbed digits, with obesity and with recurrent loss of the hair has been reported (Leven DWehn 80 541 1925).

The dominant type of congenital alopecia or hypotrichosis, with ungual, dental and other ectodermal deformations, is described under Congenital ectodermal defect. Dominant inheritance with similarities to pachyonychia was noted in cases of Scully and Livingood (ADS 47: 480 1943).

Localized congenital alopecia may be due to nevoid anomalies, such as the systematized aplastic nevus of Brauer (DWehn 89 1163 1929) in which small,

triangular patches of baldness occurred on the temple just outside the eyebrows in several members of a Dutch family. The affected members of another family similarly marked had patches not only on the temples but also on the nose and forehead (Pachur AfDuS 140 65 1930). Localized congenital alopecia also follows congenital skin defect (q.v.), linear nevi, warty or sebaceous, when they affect hairy areas, and sometimes monilethrix.



Figs. 1826 and 1827.—Congenital alopecia syndrome, showing absence of scalp hair and lateral malformation of the boy's nails. (Dr. V. Vermooten.)

Symptomatic Alopecia may be classed as follows:

Cicatricial	Noncicatricial
Burn, scald, x-ray, avulsion	Mechanical, including friction and trauma
Favus, kerion, rare types of tinea	Chemical
Necrotizing infections	Infectious dermatitis, folliculitis, tinea
Morphea-like carcinoma	Avitaminotic and nutritional
Morphea	Alopecia areata, local or universal
Hemiatrophy	Trichotillomania
Miliary cicatricial alopecia	Depilation, roentgen or thallium
Folliculitis decalvans	Alopecia following severe illness
Lupus erythematosus	Secondary syphilis, leprosy, tuberculosis
Pseudopelade	Endocrine disturbance, menopause, ...
Alopecia cicatrata atrophica	Premature and senile alopecia

Alopecia from local causes may be caused by reversible changes or by cicatricial destruction of follicles. Mechanical and chemical injuries, furunculosis, ulcerating syphilids and kerions occasionally give rise to patchy baldness. Lupus erythematosus may involve areas of considerable extent on the scalp, and the ensuing hair loss is permanent. In morphea, also baldness

is a characteristic feature of the affected areas. In ordinary tinea capitis, the hair loss is due to destruction and fracture of the hair shafts the bulbs being unaffected consequently such alopecia is only temporary Burns and scalds, radiation damage, morphea lupus erythematosus, syphilis gangrenous herpes zoster lupoid sycosis, folliculitis cheloidalis, favus kerion and other scarring diseases receive attention elsewhere Metastatic cancer in the scalp caused patchy alopecia observed by Ronchese (ADS 59: 329 1949) as did sarcoid in 3 Negro females seen by Bluefarb et al. (AD 71: 602, 1955)

While it is generally believed that destruction of the pilosebaceous apparatus implies baldness, Breedis (CancRes 14: 575 1954) observed the development of hairs in the scars of experimental wounds in the skins of rabbits wherein discs of skin had been extirpated and allowed to heal by granulation.

Cicatricial Alopecias include, among the entities listed in the preceding paragraph, dermatoses which do not cause much diagnostic confusion and others which do Laymon and Murphy (JID 8: 99 1947) clarified particularly the latter and gave clinical and histologic distinctions between pseudopelade folliculitis decalvans, lupus erythematosus and ulerythema sycosiforme They quoted Brocq et al. (AnndeD 6 1 97 209 1905) who in a detailed study classed 3 varieties (1) true pseudopelade characterized by slowly progressive baldness with an insidious onset, without inflammation or pustular folliculitis but with progressive atrophy and with hairs which, on removal show a swollen, glassy root lacking demonstrable fungi; (2) Quinquaud s type of epilating folliculitis and acne decalvans of Lailler which differ from pseudopelade by the presence of perifollicular suppuration and (3) lupoid sycosis, wherein follicular and perifollicular inflammation is so severe that pustular masses form, the tissues are necrotized and keloidal changes occur in the central parts as the regions of involvement enlarge eccentrically Laymon and Murphy reviewed and investigated the histologic changes.

PSEUDOPELADE (BROCQ) is a chronic, scarring disease of the scalp, insidious in onset, lacking visible signs of inflammation throughout its course but otherwise somewhat simulating lupus erythematosus. The multiple lesions are from 0.5 to 2 cm. in diameter with whitish, slightly depressed, atrophic centers, and sharp margins. The bald patches enlarged by gradual peripheral extension, and the disease is slowly and intermittently progressive. The cause is unknown. Alopecia is permanent. The disease evolves over a period of decades. Tonics, particul rly arsenic and cod-liver oil, have been said to be serviceable.

FOLLICULITIS DECALVANS (QUINQUAUD'S DISEASE) is a rare, follicular inflammatory process which eventually leads to circumscribed patches of hairless scar By progressive involvement f neighboring follicles the plaques gradually increase in size to form round or oval, asymptomatic lesions of from 0.5 to 2 or 3 cm. in diameter The inflammatory pustules are located at the border As active lesions involute, superficial crusts remain, which, on healing with the loss of the involved hair leave tiny red spots which gradually fade. The central region is the oldest and appears as a smooth, shiny bald scar without traces of former follicular orifices. The cause is unknown. The condition is rebellious to therapeutic effort.

Association with lichen spinulosus has been noted by Beatty and Spear (BJD 27 331 1915) and Senear (ADS 193 1920) whose 4 patients, and also the 1 of Beatty and Spear were women who had had the scalp condition for some time before the widespread rash appeared. There always exists the diagnostic problem in scarring folliculitis of the scalp d stinguishing tinea capiti due to the *Trichophyton tonsurans* group (p. 500)

LUPUS ERYTHEMATOSUS (q.v) when it involves the scalp begins with small, wine-red, non diagnosticable flecks around th follicles. These gradually enlarge and coalesce in irregular plaques. While such lesions may remain superficial and erythem tous, they re more likely to become slightly depressed, showing central atrophy with palle and peripheral redness with ctivity Scaling is similar to that of discoid l pus erythematosus in other locations, and conical plugs usually remain in the dilated, atrophic follicles. Telangiectases are present both at the borders and in the centers of the plaques.

ULERYTHEMA SYCOSIFORME begins almost exclusively on the face, anterior to the ear It is usually unilateral. It is extremely rare and occurs on the scalp only by extension. Inflammation and infiltration are highly accentuated, the early lesions bei g large peri follicul pustules which tend to coalesce. The underlying skin is red, thick, and frequentl covered with crusts and scales. Extension is centrifugal. Centrally there re complet atrophy of the pilosebaceous system and keloidl ke scarring

See Brocq (BerlinSocMHôp 5: 299, 1888, Traité élémentaire de dermatologie pratique Doin, 1907, ed. 2, p. 648) Quinquaud (BerlinSocMHôp 5 336, 1888 AnndeD 10 99 1889) Photinos (La Pseudopelade de Brocq, Maloine, 1930, 481 pp.); Barbalis and Beijerinck (DWchs 99 1, 1934) sycosiforme in scalp, vaccine therapy Stuhberger (ADS 49: 151, 1944) Goodman

helped a case with vitamin A. Curth (JID 13, 231, 1949) girl with chondrodystrophia calcificans also. Laymon (ADS 62, 181, 1950) histologic studies of scaly dermatoses of the scalp, distinctive in lichen planus and lupus erythematosus.





Fig. 1328.—Pseudopelade (Brocq) (Dr Costa Riehl)
Fig. 1329.—Pseudopelade. (Dr O. G. Costa)





Figs 1330 and 1331 — Folliculitis decalvans (Quinquaud)

ALOPECIA LIMINARIS FRONTALIS (SABOURAUD) begins in front of the ears, generally in young women at about 13 years of age preceded by little rust like those of pityriasis steatoides but the ha r f lls out a d is never replaced. The disturbance is symmetric and it spreads across the f rehead so as to join the l iltially prea ricular zones of is al reat only the anterior ma gin of the scalp is affected, and the remaind r of it stays normal

The condition results in alopecia in which the cicatrization is hard to detect. Its progress may be arrested with sulf r ointment but the hair loss itself is permanent. Compare Traumatic marginal alopecia.

ALOPECIA CICATRICIELLE MILIAIRE occurs in old, seborrheic scalps, particularly in women, according to Sabouraud (ArchdaD : 446, 1931) and leads to the production of multitudes of tiny scars scattered irregularly about the scalp, each corresponding to 3 or 4 hairs. It involves the vertex as a rule, and must be distinguished from sycosis, from pseudopelade, and, with considerable difficulty from neurotic excoriation. If lichen sclerosus involved the scalp, it would produce a condition resembling this, so that estrogenic therapy deserves trial. Compare discrete lichen simplex of the scalp in hypoproteinemia. (p. 870)

ALOPECIA INDURATA ATROPHICA was the name given by Pincus (BerlKlinWchs 1883 p. 645) for a sclerosing form of scalp disease affecting the vertex particularly of women. It is often familial in it incidence It causes cohesion of the connective tissue with th underlying aponeurosis so that peculiar hidebound condition of the scalp results, along with diffuse baldness of variable degree, even total. Sabouraud described this as Alopécie dite d chignon, wiglike as it is in its distribution. It is associated, i my experience, with arteriolar sclerosis and nephritic hypertension, and I suspect it is due to vascular disease with resultant malnutrition of the hair

FOLLICULAR ATROPHODERMA AND PSEUDOPELADE has been reported in association with chondrodystrophia calcificans congenita by Miescher (Dermatologica 89: 33, 1944) a curiosity reviewed, with the presentation of 3 cases, by Curth (JID 13: 233, 1949) Atrophic alopecia occurred in spots on the scalp, and on the extremities and trunk were irregula zones i which dimple like depressions were found at the place of follicular orifices. Curth found other defects such as incontinentia pigmenti, cataracts and polydactylia in some members of the family in which there were several cases of the queer syndrome. Th scleroderma like lesions of the scalp have been seen in inco tl entia pigmenti, indistinguishable Curth said, from th ones she noted. The skeletal changes are of chondro-osseous dystrophy with punctate epiphyseal dysplasia. The syndrome has been observed only in females.

Noncicatricial Alopecias to be considered are as follows

MECHANICAL ALOPECIA implies simply the breaking off of the hairs through manipulation, such as the friction of the infant too young to sit, against its bed. Hairs are more fragile in some persons than in others. The application and removal of medicines applied to the scalp may in itself occasion traumatic alopecia (Bowers BJD 62 262, 1950) Depilation is discussed with tinea capitis, treatment of hirsuties (p 1328) and chemical removal of hair (p 1339)

Alopecia thought by Beeson and Pickett (ADS 28 53 1933) to be trophic resulted in cats when the second cervical spinal ganglion and roots were cut That this operation of Joseph gives rise to peripheral pruritus and hyper esthesia was shown by Aubrun (ADS 34 564, 1936) The animal scratches the skin so that patches of traumatic alopecia result.

TRAUMATIC MARGINAL ALOPECIA results when traction from a tight coiffure causes hair loss about the margins of the scalp (Spencer ADS 44 1082 1941 Costa and Junqueira ADS 48 527 1943; Costa BJD 58 280 1946 Kam et al. ADS 60 905 1949) If the hair is more than normally fragile as a result of hereditary or of endocrine or nutritional disorder the mechanical agency is more influential. The disorder may be seen in white women as well as Negroes (Ayres et al. ADS 60 1116 1949) Overzealous medication and washing can cause alopecia. A young woman seen by Sharlit (ADS 54 601 1946) brushed her crown until it was almost bald. Alopecia of men s legs appeals to me as being of frictional origin.

CIRCUMSCRIBED HYPOTRICHOSIS OF MEN'S LEGS.—Under the title f Atrophic Skin in Men, Robertson (BJD 50: 581 1938) reported studies of the st te of the skin and hair of th legs and scalps of 1,171 men between 20 and 60 years f age In many adult men, there occurs on the legs an area of skin with the following characteristics: (1) It is smooth, shiny and hairless and has no goose-skin appearance on exposure to cold; (2) it is wh ter than normal skin and looks thi d trophic; (3) it occurs below the knee on the anterolateral and posterior aspects f the leg and varies in size in different individuals (4) its position and extent on one leg are the same as on the other (Castellani noted unilateral involvement and claimed to h ve seen th disorder affecting the thighs and the arms, as w ll as the shins); (5) in ppearan ce and texture it is simila to th skin of diff se lopecia f the scalp; (6) it does not occur before puberty; and (7) except on the scalp, no similar area occurs elsewhere on the body

It was found that the majority of men who were bald on the scalp, 379 f the 1,171 men examined, were bald also on the legs, 403 of the entire group. There was normal sensibility to touch, heat, cold and pain. The " oclfensor" reacti n after injury was the same as in normal skin. The reaction to pricked in 1:1000 epinephrine a d 1:1000 histamine acid

phosphate was the same as of normal skin. As in diffuse alopecia of the scalp, so also in this cutaneous atrophy on the legs, the hair loss and the cutaneous atrophy were bilaterally symmetric and when there was baldness of the scalp there was generally baldness of the legs. These observations suggested a common causation, a general change occurring in the body involving factors of vascular supply nerve supply and influences, and the composition of the blood. It appeared that the change in the body which was responsible for diffuse alopecia of the scalp and for the areas of the cutaneous atrophy on the legs was an alteration of the balance of endocrine secretion and dependent on the integrity of



Fig 1832.—Traumatic marginal alopecia.

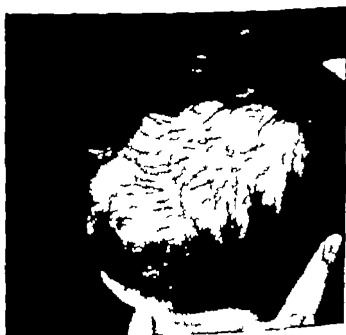


Fig 1833.—Trichotillomania.

the testicles Robertson believed. How this produces the cutaneous atrophy and why the area affected should be localized on the scalp and legs are questions yet unanswered (Ronchese and Ch[illegible] ADS 40: 416, 1939) Robertson did not believe that friction of the trousers on the skin is influential, or that tightness of the garters is involved, or that the habit of crossing the legs plays a part. Tommasi (BJD [illegible] 1940) thought the d[illegible] to be concerned with a neuro arthritic diathesis. Practically the condition is of [illegible] quence.

CHEMICAL REMOVAL OF HAIR.—Hair straighteners often used by Negro women generally contain sodium hydroxide in an ointment base, to be applied warm with a heavy comb (Anderson ADS 62 910 1950) This weakens the shafts so that they may readily break off.

The waving of hair (see Dermatitis venenata cosmetic) requires that keratin be made soft and plastic for a time If the solvent agent is allowed to act overlong the hair will break off Cases were described by Reiches and Parker (ADS 66 521 1952) caused by cold wave thioglycolate they have been seen by every dermatologist who has practiced during the time that amateur home-waving especially has been popular No harm is done by mere dissolution of hair save temporary cosmetic embarrassment It regrows normally

EXPERIMENTAL DEPILATION.—The depilatory action of intermediary polymers of chloroprene was studied by Flesch and Hunt (ADS 65 261 1953) and Flesch and Goldstone (Sci 113 126, 1951 JID 18: 267 1952) These compounds, used in the manufacture of synthetic rubber had been observed to cause temporary depilation of workers. Flesch et al. attributed the property to the ability of the chemicals to inactivate sulfhydryl because of the presence of carbon atoms joined by double bonds, and they tested depilatory effects of compounds lacking chlorine but containing the linkage.

A single application of allyl laurate, of allyl benzoate of allyl diphenylacetate, or of squalene, or repeated applications of vitamin A caused reversible hair loss at the site of application. All of these except vitamin A inactivated free sulfhydryl groups of glutathione in vitro. Human sebum containing substances of this kind, may they thought, when abnormal, be related to disorders of hair growth, keratinization and alopecia. Human sebum, its nonsaponifiable and saponifiable fractions, and 3 of its unsaturated components (squalene oleic acid and linoleic acid) are potent local depilatory agents when applied to the skins of laboratory animals (Flesch: ADS 67 1 1953)

TRICHOTILLOMANIA is a neurotic habit of pulling out hair (see p 818)

EMOTIONAL SHOCK is said to have been followed by total defluvium which was temporary This is doubtless a form of alopecia areata (p. 1341)

TOXIC OR FEBRILE ALOPECIA commonly accompanies typhoid fever influenza, pneumonia septicemia and other severe sicknesses. The hair is considerably thinned, sometimes lost. Prognosis is good after recovery from the primary illness. Alopecia may result from the toxic action of drugs thallium is used for the purpose in tinea capitis (q v) Thyroid antagonists such as propylthiouracil may cause hair loss. It was noted after anticoagulant therapy (Thrombocoid and Dicumarol) by Gischer et al. (SchweizMWchn 83 509 1953) Exfoliative dermatitis, whatever the cause and it is sometimes due to drugs, results in various degrees of hair loss, abetted by the friction to which the irritable skin is subjected.

Alopecia of motheaten appearance involved the occiput in children recently bitten in that location by the tick, *Dermacentor variabilis* observed Ross and Friede (AD 71 524 1955)

CACHECTIC ALOPECIA is a frequent condition in tuberculosis, and may occur in diabetes mellitus, rickets, and other wasting disorders. The hair loss is qualitative as well as quantitative the few new hairs in the regrowth usually being finer and more lanugo-like than the old. Complete recovery may or may not take place Syphilis causes cicatricial alopecia by gummatous destruction or cutaneous atrophy In the secondary stage syphilitic folliculitis may cause temporary hair loss which may or may not be permanent. Leprosy may provoke hair loss through actual leprous infiltrations of the follicles. Iron deficiency is the common cause of diffuse alopecia in women.

NUTRITIONAL ALOPECIA.—See also Avitaminosis, and Starvation. Vitamin A, antagonistic to thyroxin, seemed helpful in reducing hair loss in thyrotoxicosis, reported Schwemmler (MünchenMWchn 86 1226 1939) and it stayed the loss in pregnancy (q v) although it had no apparent effect on growth of nails. Patchy alopecia in an Arab responded to vitamin A therapy (Gill ADS 51 110 1945) Diffuse hair loss as well as depigmentation in avitaminosis in children is reversible if the patient survives following the administration of adequate diet and polyvitamin mixtures, stated Chavarria et al. (J 132 570 1946) the changes in adults were similar but not so severe as in children. The hair was especially vulnerable to traction in the poorly nourished children of

Berlin, whose skins were lusterless and thin, noted Fleck (DWchn 123 87 1951) Marginated frontal and temporal alopecia was noted in young Negroes in association with sickle-cell anemia by Cornbleet et al. (ADS 59 519 1949).

ENDOCRINE DISTURBANCES associated with loss of hair are varied and complex. In pituitary emaciation there is loss of hair from the pubic and axillary regions the eyebrows, the lashes and the scalp (Plummer and Jaeger ANeurol 40 1013 1938 Wahlberg J 106 1908 1936) Other features are anorexia, constipation amenorrhea, hypotension and hypothermia. Simmonds disease (Escamilla and Lisser JClinEndocrin 2 65 1942) and progeria (Moehlig J 132 640 1946) are associated with gray and scanty hair See Skin manifestations of endocrine disorders (p 692) and Pregnancy (p. 703)

Hypertrichosis of the distal extremities and partial or finally complete alopecia of the vertex are characteristic of the pathogenic pituitary gland. Hypopituitary alopecia begins at the frontotemporal angle with gradual recession of the hairline along the temporal ridge, until finally the entire vertex of the head is bald with residual growth along the lateral or marginal scalp, according to Engelbach (Endocrine Medicine Thomas 1932, vol. 3 p. 808)

The hypotrichosis of the eunuchoid or hypogonadal individual characteristically does not affect the scalp which is usually covered with long coarse hair, in contrast with the loss associated with acromegaly Total alopecia in a young child, which came on following chicken pox, was treated with stilbestrol ointment, following which vaginal bleeding and the appearance of secondary sex characters developed reported Whittle and Lyall (BJD 61 133 1949)

Total alopecia preceded operation for hypernephroma in the patient of Schill (Endocrinol 24 572, 1939) and the hair regrew after the tumor was removed. Schill discussed the possible feminizing influence of some adrenocortical tumors, as has also been noted by Armstrong and Simpson (BMJ 1: 782, 1948) who reviewed 7 cases in males and reported 1.

Androgenic substances caused partial loss of scalp hair often associated with hypertrichosis elsewhere noted in 22% of the patients with carcinoma of the breast treated with male hormone by Kennedy and Nathanson (J 152 1135 1953) Hair of the scalp became dry and coarse and fell out when it was combed. When use of the hormone was stopped hair regrew in the areas from which it had been lost. They believed that androgens produce alopecia primarily in persons who have a hereditary predisposition to baldness, as indicated by experiences in eunuchoids given androgen therapy Androgens in their patients also provoke milia, comedones and acne, seborrhea, diminution in brittleness of nails and a ruddy flushed complexion resembling that seen in Cushing's syndrome A malignant seminoma of the testis caused baldness and acne which improved after castration and became worse when metastases developed in the man reported by Murrell and Pepple (ADS 57: 930, 1949)

Melancholia along with senile involution is often accompanied by hirsuties, thinning and coarsening of the scalp hair and loss of weight and of appetite (Allen and Carlyle-Gall BMJ 2 67 1949) Increase in general pigmentation and hirsuties are commonly seen in depressed psychopaths.

Hypothyroid baldness begins along the margin of the scalp oftenest about the temporal regions, less frequently at the occiput, rarely extending to the vertex unless in a terminal complete involvement. Alopecia of this type can be caused by thiouracil (Wilburne J 147 379 1951)

SEBORRHEA.—Among the chronic inflammatory scalp disorders which may be imagined to give rise to hair atrophy and hair loss seborrhea (q v) and seborrheic dermatitis (q v) are usually inculpated. Alopecia pityroides first involves the temporal and frontal regions, and is accompanied by more or less furfuraceous desquamation. Regression of the hair line in lateral V's is progressive and a circular patch of thinning enlarges over the crown. The denuded areas with feeble lanugo where hair once thrived slowly approach one another leaving a forelock in the middle of the frontal region This goes too, in time and a fringe alone surrounds a glistening pate

ALOPECIA SENILIS, associated with old age is characterized by symmetric thinning of the hair on the vertex and in the temporal regions, although occasionally nearly the entire calvarum is involved. Its appearance and course

do not differ from seborrheic or premature forms except in age of onset (Rattner ADS 44 201 1941) The hair loss is usually gradual and a downy growth, with more or less accompanying evidence of seborrhea, may persist for months after the disappearance of the pigmented shafts. There may be associated thinning of the hair in the axillary and pubic regions. Histologic studies by Light (JID 13 53, 1949) suggested a relation between the number of hairs and the age of the individual, and also the amount of connective tissue infiltration in the fat layer about the hair roots.

Alopecia Prematura is that form of acquired baldness which resembles alopecia senilis but occurs without determinable cause in relatively youthful individuals. Premature alopecia appears to indicate masculinity because children, females, and eunuchs do not exhibit it (Hamilton AmJAnat 71 451 1942) Baldness occurs more frequently in men with relatively heavy growth of body hair (Harris BJD 59 300 1947) Hoping to feminize an experimentally inclined and balding physician friend and so to alter the course of his alopecia, I once administered stilbestrol, when the chemical had been newly invented, and its effects were, to use an understatement, unsatisfactory The tendency to premature baldness is inherited in at least some cases, ex emplified by the family tree presented by Templeton (ADS 44 312, 1941) wherein the trait was transmitted through the females, not through the males. The aphorism is ascribed to Rattner that, The man who would avoid baldness should exercise great care in the selection of his grandparents. Calcification of the skull was the explanation not facetiously given by Hoelzel (J 119 968 1942) and fluorine was incriminated by Spira (JHyg 44 276, 1946) whose logic was not Aristotelian. The fat loss theory of balding could not be reconciled with the finding of normal thickness of the scalp in cases of premature baldness by Garn et al. (ADS 70 601 1954)

A review of the hypotheses regarding pathogenesis was given by Szasz and Robertson (ADS 61 34 1950) who submitted the suggestion that, judg ing from psychoanalytic interpretation of the facial expressions of the balding individual, chronic tension of scalp muscles produces shearing stress in the dermis and consequent ischemia results in defluvium, to be treated, perhaps, by blocking the branches of the seventh cranial nerve. According to the report of the Committee on Cosmetics (J 139: 840 1949) The claims of anyone that he has developed a remedy for the control or cure of baldness should be viewed with the greatest skepticism.

Since masculine alopecia is of unknown etiology is compatible with an existence successful in every respect, and is irremediable, I advise the sufferers who seek my aid to accommodate their ego to their destiny

ALOPECIA AREATA

Bald patches develop suddenly on otherwise apparently normal skin. They range greatly in size being rounded areas which sometimes overlap. The scalp is the site of predilection although the eyebrows bearded region, pubes axillae and any part of the body may be involved. Sometimes the first in timation of the disorder is the sudden detachment of a large bunch of hair Occasionally the outfall is gradual several days being required for the de velopment of appreciable baldness. The spots enlarge peripherally for a few days or weeks. Loose shafts may exhibit atrophic changes near the mouths of the follicles their altered shape more or less justifying the title, exclama tion point hairs; and many of these can be extracted easily and painlessly during the spreading stage of the attack. During the period of progression, hairs at the periphery of the patches are loose and can readily be extracted When peripheral hairs no longer come out when one pulls at them gently one may predict that further extension of the patch in that direction is at an end.

Ophiasis is the clinical type that involves the margins of the scalp partly or entirely usually beginning in the mid-occiput and spreading behind the ears in a horizontal symmetrical band seldom exceeding 1 to 3 cm. in

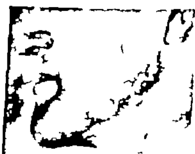


Fig. 1834.—Alopecia areata.



Fig. 1835.—Alopecia areata.





Figs. 1836 and 1837.—Alopecia areata involving the beard.

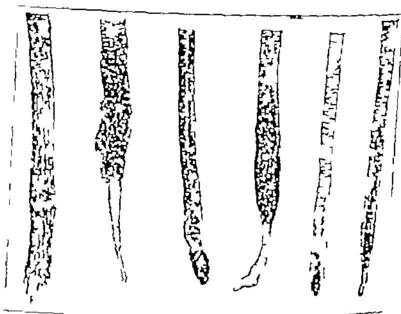


Fig. 1838.—Marginal loose hairs from alopecia areata. (Dr. A. R. Robinson.)



Fig 1839—Loss of eyelashes in alopecia areata.







Fig. 1840.—Alopecia areata with white regrowth. (Dr J Lamar Calloway)
Fig. 1841—Alopecia areata with white regrowth. (Dr O. G Costa.)
Fig. 184_.—Alopecia universalis. (Dr Robert M. Andrade.)

width (Troxell ADS 70 812 1954) The patient is usually a child, and alopecia areata in infants generally assumes this form in which the prognosis is worse and the likelihood of relapse greater than in ordinary alopecia areata.

Alopecia universalis is the type wherein the skin becomes completely denuded of hair Universal involvement fortunately is rare for it carries a poor prognosis.

In ordinary cases of alopecia areata, regrowth takes place slowly The first crop of hair is usually thin, white and lanugo-like and is likely to fall out after the shafts have attained a length of 1 cm. or so. The second or *third regrowth usually persists. Regrowth is less likely in older patients* and when large areas are involved, and loss of hair may be permanent. The regrown hair usually regains its normal color eventually but it may remain white for a long time sometimes permanently

Associated disorders, such as vitiligo are sometimes present both on the affected areas and on other parts of the body Nail changes, generally in the form of transverse white stripes, also are occasionally noted

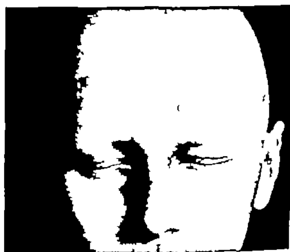


Fig. 1343 —Alopecia universalis in a girl 12 years old, with no other detectable abnormality (Dr Harold N Cole.)

Posey (TrAmCollPhys 40: 336 1923) called attention to the association of poliosis with poliosis of the eyelids. Tomkinson (BMJ : 518, 1934) and others have reported a relationship of alopecia areata with strabismus and other ocular troubles, sometimes occurring in familial groups. See Vogt Koyanagi syndrome described in connection with uveitis sometimes with retinal detachment, dysacousia, vitiligo poliosis and alopecia are collectively seen occasionally in 1 patient, and such cases constitute this fairly well defined group.

Etiology—The cause is not known. The disease affects the sexes with about equal frequency and is commonest between the first and third decades of life A boy 15 months old had 2 patches on the back of the head, and regrowth was already beginning when Warren (ProcRoySocM 31 54, 1937) observed the case

Anxiety nervous shock and emotional fatigue are surely connected with the causation in some manner Time after time I make the clinical observation that the onset of alopecia areata coincides with death in the family business failure getting married or getting divorced. Rogers (J 93 019 1929) saw *a man whose alopecia areata recurred every* time his wife had a child. Total alopecia followed a criminal attack upon a girl seen by Sabouraud the hair grew back. Psychiatric aspects were considered by Peck (GeorgiaMJ 37 226 1948) to whom the disorder suggested a conversion syndrome See Psychosomatic aspects of dermatology regarding the hole in the head concept A patient is as well served therapeutically with reassurance as with medication believed Arnold (ADS 66 191 1952)

Typical lesions sometimes develop as a result of tra matic neuritis. Ronchese (ADS 28: 639 1933) reported an instance of transitory baldness of a peculiar type following trauma. Sutton, Sr noted alopecia areata following supraorbital herpes zoster Occasional epidemics have been reported by Bowen (JCutD 33: 343, 1915) Abscessed teeth and hyperplastic or infected tonsils are often associated. Grindon (JMoMA 15 145, 1918) emphasized the frequent finding of amalgam and gold fillings in the same mouth in patients with the disease, as well as decayed teeth and other stomatic irritants.

Many patients promptly regrow their hair and feel much bett r when gi en thyroid extract. The hypothyroid individual is made wearier by a given task than a normal one is, and his worries promote insomnia despite his tired feeling which he generally ttempts to relieve with caffeine Many patients lose their nervousness and sleep better as soon as they stop coffee and tea and commence taking thyroid medication, which must of course be given a correct dosage as described under treatment of acne No proof f endocrine etiology could be discovered in universal cases by Walsman and Kepler (J 116 2001, 1941), nor in a series of 230 patient could Walker a d Rothman (JID 14 403 1950) find evidences of endocrine abnormality

In an extensive study of 114 cases, of which 84 were ordinary and 24 total or u i versal, Anderson (BMJ 2: 1250 1930) found a previous history of the disease in 23% and a positive family hist ry in 19% Mental trauma appeared to precipitate the condition i 23% of the patients. There was no relation to sex or hai color The disord wa common r in the younger age groups. Nail changes were common in the extensi e cases. Vitiligo was present in 4% About 1 case in 100 proved permanent, and the prognosis was worse when the disease began before age 10 ears.

The hypothesis th t th disease i directly due eithe to tinea, as o ce suggested by Crocker or to syphilis, a once claimed by Sabouraud is no longer creditable. The bacterium described by Vaillard a d Vincent (An InstPasteur 4: 446, 1890) has no proponent now Wright and Harkin (ADS 19: 363 1929) concluded that lopecia areata is not a trophoneurosis and suggested that it origin i concerned with vasoconstriction. Sabours d's suggestion that it may be a result of i hibition of the function of the hair papilla, this, turn, being due to some malfunction of the sympathetic system, is not incompatible with Wright's views. Dermatoscopic investigations by Levy Franckel and Juster (AnndeD 9: 785, 1928) showed diminution of the capillaries and arterial spasm, and these authors believed that angiospasm is a essential etiologic factor Brown (BJD 41 290 1929) and Roxburgh (BJD 41: 351 1929) believed that some etiologic relationship exist between lopecia reata a d vitiligo, and, possibly also scleroderma. Genner (Alopecia Areata Le in & Munskaard, 1929) likewise emphasized the coincide ce of alopecia areata and vitiligo and the frequent occurrence of exophthalmic goiter in these patients. Wilson and W kelman (J 86 14.4, 1926) found a brain tumor ove the pituitary in a case of generalized lopecia examined post mortem. Only 3 of 33 heads examined radiographically b Stri kler and Greenberg (ADS 37: 1008 1938) deviated from n rmal with regard to the shadow of the sell turcica, and their study re ealed no interconnection between detect ble pituitary disease and al pecia reata.

H redity is probably a factor Cockayne t tes that the disease almost always affects person with darkly pigme ted hair so that th re is probabl a linkage between the gene for liability to the disease a d the genes for dark hai ; that is, they are probably carried by the same chromosome Sabouraud (An deD 1910 p. 545) noted that 22 of 81 cases ga e a history of the occurrence f alopecia areata in othe members of their family Th fathe uncle d patern l grandmother f the child reported by Warren (1937) had had t. The disease was total in father and d ughte n a report by Sh lton and Hollande (ADS 46 137 1942) Alopecia areata affected 3 members in each of 2 families noted by Bereston and Robinson (ADS 64 204, 1951) Identical twins manifested it, both in occip tal location reported Hendren (ADS 60: 793, 1949)

Pathology —Atrophy of the follicles is progressive according to Sabouraud and is complete only in some follicles after many attempts to regenerate the hair therein. The attempts are accompanied by irregular budding and proliferation of the follicular epithelium in areas where new hairs are produced but many of them are destined to be cast off. Eventually the surface epithelium of the hairless areas becomes atrophic and the pigment content of these cells disappears. Follicular atrophy may be accompanied by atrophy of the sebaceous glands to such an extent that the whole follicular apparatus seems to have disappeared. In cases simulating the seborrheic type of alopecia, ending in baldness the sebaceous glands are hypertrophic despite the almost complete disappearance of the hair follicles.

Prognosis.—The outcome is favorable in inverse proportion to the extent of the baldness and the age of the patient Relapses are frequently seen and recurrences are common, but in young adults complete recovery can usually be safely predicted in all but universal cases, which are likely to be permanent. In patients under 10 and over 40 years of age the outlook is less promising and the prognosis should be guarded.

Treatment.—Many patients promptly regrow their hair and feel much better when given thyroid extract (Baukus et al. NYSJM 36 1629 1936). Cortisone is of great value. Arsenic, iron, cod liver oil, diuretics, cathartics, hexamethylenamine and other *medicines* have been given empirically.

Phenol, swabbed quickly over the area then wiped off with alcohol, is popular (Bechet ADS 44 512, 1941). Rubbing on a benzyl benzoate emulsion does at least as much good (Robinson and Robinson SouthMJ 47 894 1954). Rubefaction with ultraviolet light *justifies* more or less enthusiasm (Peterkin MP &Circ 201 520 1939). *Anthralin* was so used by Goodman (ADS 40 [illegible] 1939).

Rest and relief from *anxiety and fatigue* are essential. Focal infection should receive attention (Grace ADS 45 349 1942).

Pituitary extracts may encourage regrowth (Thorner Endocr 26 [illegible] 1940). Androgenic substances deserve a try, thought Stalder (Dermatologica 86 262, 1942). *Cortisone* by mouth given by Dillaha and Rothman (J 150 546 1952) induced *patchy* regrowth in 16 of 22 severe cases when given for 10 weeks or more. *ACTH* given in 3 cases of universal alopecia promoted regrowth which continued *only* as long as the hormone was continued, reported Wilson (Lancet 1 646 1952). The experience of Wainger and Cappleman (ADS 66 397 1952) was similar. Two women I have seen with total alopecia of the scalp regrew hair satisfactorily when cortisone was maintained in a dose of 75 mg per day.

Foreign protein therapy may be undertaken. Marcoglou (ADS 33 1[illegible], 1936) approved the treatment suggested by Djorit h, who injected sterile milk intradermally about the circumference of the lesions.

Small astigmatic errors are frequently *found* when patients are refracted, and correction of these is often *followed* by regrowth of hair according to Haynes and Parry (ADS [illegible] 340, 1949).

Roentgen therapy in *epilating* dosage applied to a particular field of the scalp in a case of universal alopecia was followed in 6 weeks by regrowth of hair in that field and not elsewhere as *reported* by Leipold (DWehn 103: 1259 193). Grenz rays were likewise effective in 6 weeks in 40 cases treated by Last and Stein (APhysTherapy 193[illegible] p [illegible]) with doses sufficient to provoke hyperemia, some 800 to 1,000 r. MacKee (X-rays and Radium in the Treatment of Diseases of the Skin Lea & Febiger 193[illegible] p 531) was hesitant to accept the trustworthiness of report that x rays stimulate hair growth. I am even more hesitant than he. Thorium X and ultraviolet were used by Feeney (BritJDerm 10 146 194) with good effects he reported.

GRAYING OF THE HAIR

Congenital Canities is rarely complete but it occurs in albinism and occasionally in persons with an otherwise normal integument. Congenital patchy canities is *less rare* and may exhibit a strong hereditary tendency (Nusser Lancet 2 947 1938). The lock of white hair is often placed conspicuously on the frontal scalp, poliosis circumscripta.

Acquired Canities may develop rapidly or slowly. Canities senilis is the ordinary senile type; canities prematura is the type which has its onset early. Premature grayness manifests itself early with a few gray hairs in childhood, a sprinkling of them during adolescence, and complete grayness by the age of from 25 to 30 years. This is often a familial trait and appears sometimes as a simple dominant character.

Graying may be symptomatic. It occurs in endocrine disturbances, particularly thyroid troubles. It is typical for regrowth of hair in alopecia areata to be white at first but as a rule normal pigmentation is eventually regained. Rats on a diet low in vitamin B filtrate factor develop symmetric patterns of graying; an antigray hair factor, p-aminobenzoic acid (Sieve Sci 94 [illegible] 1941) exists in liver and yeast. The rat antigray hair factor failed to help human beings (Reinhauer ADS 49 132, 1944; Brandaleone et al. AmJMedSci 208 315 1944) and calcium pantothenate was without value in restoring hair color in the experience of Kerlan and Herwick (J 123 391 1943). Nutritional deficiency (q v) productive of depigmentation of skin and hair in human beings has been described in children in Malaya (Nicholls: Lancet [illegible]) and in Africa (Hughes BMJ 2 [illegible] 1946). A rat poison derived from thiourea

causes loss of pigment and cessation of hair growth in the rat (Richter J 129 927 1945) Exposure of the whole body to x ray in experiments with mice resulted in depigmentation of the hair the severity of which paralleled the dose quantitatively so that the correlation might actually serve for biometric measurement observed Moshman and Upton (Sci 119 186 1954)

Canities of the eyelashes was the unusual sequel of dermatitis of the eyelids in a young woman seen by Frost (ADS 48: 324 1943); see Pape (ZentrlblHautkr 29: 619 1909) It is not remarkable when this occurs in association with vitiligo and it is seen in the Vogt Koyanagi syndrome (q v) well described by Hague (AOphth 31: 520 1944)

Return of colo to hair which has become gray has been observed. Ronchese (J 117: 1140 1941) saw this in a man whose hai was white until prolonged terminal illness, during which it gradually returned to black. Isdell (MTimes&Gaz 2: 680 1894) told of his f the whose hair regained its natural dark color in his later years during which he was in good health. A case was cited by Jackson and McMurtry (Diseases of the Hair Lea & Febiger 191., p. 60) wherein the scalp and beard hair changed suddenly from dark to white gradually regaining it color several times. Return of colo is said to be not uncommon in diabetes mellitus afte the patient becomes controlled and well nourished (QMN J 137 229 1948) Acquired anities in a child I treated responded to thyroid.

Whiteness of hair is due to failure of pigme t formation in the follicle before ornification takes place (Strong: A atRec 14 63, 1918 Sci 54: 356 1921) Dopa positive cells are absent from the region of the follicles. Physiologic and anatomic facts are incompatible with the possibility of actual, nonartificial, instant blanching Spotty depigmentation followed a motor car accident within 7 weeks in the patient of Macleod (BJD 49 437 1037) Blanching must be a slow process, although the topic of sudde blanching, howeve dubious, is peren ially of i terest (QMN: J 1 1 161 1943)



Fig 1444—Poliosis circumscripta, acquired in the course of development of vitiligo.

No treatment is necessary The use of hair dyes, which may contain silver nitrate, pyrogallic acid or paraphenylendiamine, is frequently injurious see Redgrove and Foan (Hair Dyes and Hair Dyeing, Heineman, 1939) Dermatitis venenata cosmetic; Anatomy pigment; Vitiligo Albinism.

Discolorations of the Hair through cosmetic efforts and accidents were discussed by Goodman (Professional Beauty Culture, McGraw Hill, 1937) Burns and scorches are not especially rare. Green or black discoloration may follow the use of a mercurial lotion and a permanent waving device (Philipsen UgeskfLaeger 95 746 1933 Gray and Klaber J 107 598 1936) Medicines which stain blonde hair objectionably include resorcinol, chrysarobin and Anthralin. Potassium permanganate stains will wash out

RING HAIRS (PILI ANNULATI RINGELHAARE LEUKOTRICHIA ANNULARIS)

R nglike grayness of the hair is a peculiar disorde in which many or all of the hairs of the mustache or scalp exhibit achromic ri gs alternating with pigmented ones. Aside from the pigme tary changes, the filament are apparently norm l (Kll ke: Bloch's Hbch 160: ", 1925) Th co dition is probably analogous to transverse bands of nails (q v) representing alternate st tes of good and poor n trition of the growth zones of the follicles; compare gift spots in nails.

The disorder is a rare one. Crocker (BJD 5: 175 1893) reported its occurrence in a girl and referred to a patient he had seen in which the mustache was affected. "Besides these two cases of my own," he wrote "I only know of that of Erasmus Wilson, the case of which the hair is in St. Bartholomew's Hospital Museum, and that of Karsch, recorded by Landois. The case of E. Lesser recorded as a case of ringed hair from Fig 3 of his plate, is evidently referrible to moniliform hair." Galloway (BJD 8 437 1896) saw the condition in 2 young brothers. Cady and Trotter (ADS 6: 301, 19**) found 1* cases in the literature and described a number of examples occurring in 2 families. They ascribed the appearance to the presence of gas-filled interstices in the cortex and medulla of the hair and they found no evidence of lack of pigment or of atrophy thereof. Monilethrix was also present in the patient presented by Sweitzer (ADS 10: 121 19*4). A young man, whose mother and several of her relatives and whose sister and brother were also affected, was presented by McCleary and Montgomery (AD 71: 526 1955)

See Landois (ArPath 35 575, 1866); Brayton (IndMGaz 14: 10, 1897), Riecke (ZentrblHuG 5 437, 1922) v West (NederlTijdGeneesk 1 1186, 1929), Galewsky (HandbHuG 11 1 169 1932, Springer) Montgomery and Binder (ADS 58: 177 1948) sisters affected since birth.

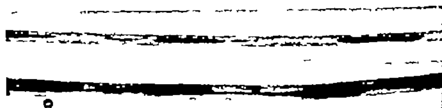


Fig. 1848.—Ring hairs (Dr Fred Weidman.)

THE NAILS

NAIL GROWTH AND MANIFESTATIONS OF ABNORMALITY

Nails are analogous with hairs in their embryology structure and physiology. Picture a hair which grows from a point and is set perpendicularly in the skin, transformed into a structure which grows from a transverse line and is set so obliquely that it extends as a practically horizontal plate. As the hair grows so grows the nail with the geometric analogy that the hair is the extension of a point that is a line and the nail plate is the extension of a line that is, a surface. Produced as the nail is by a line it extrudes like the roll of a player piano. What alters its source registers a corresponding mark on the plate.

The growth zone of the nail is a line curved convex distally. It is a curve parallel with the distal margin of the lunula. Beau's lines are transverse bands representative of temporary damage of the entire growing zone and they parallel this curve. A band across the nail curved concave distally could not result from a systemic influence. It is due to a dermatitis of the dorsum of the terminal phalanx or to trauma usually from manicuring (Netherton J 93 1116 1929)

The close relationship between growth of hair and growth of nails is illustrated in alopecia areata (q v) in severe cases of which nails as well as hairs may be shed while in milder cases, marks on the nails may coincide with activity of the abnormal process. Congenital ectodermal defect (q v) generally manifests both hair and nail disorders. The nutritional status of the patient is reflected in both hair and nails, for one finds both to be thin and brittle in iron deficiency malnutrition and various hormonal and nutritional dyscrasias. A review of nail changes associated with internal disease was provided by Weiss (SchweizMWschr 73 91 1943). In many cases of pulmonary tuberculosis Banyai and Cadden (ADS 48 306 1943) noted a tendency to diminution of width of the lunula or even the disappearance of it especially in cases with complicating silicosis.

The epithelium of the nail bed is so disposed as to grow distally as well as superficially as it proliferates. This feature is found too in the epidermis of the lateral nail folds where cleavage is such that hangnails (q v) form when the epidermis is torn. In the basal epidermis of the nail, distal growth

is attested by the fact that if a mark is made upon it after surgical removal of the nail, the mark grows outward ahead of the new nail evolving from the root. If subungual hemorrhage stains the depths of the nail plate the discoloration grows out with the nail. The nail plate is to some extent dependent on the underlying bed, for when separated from it the plate becomes cloudy discolored and perhaps distorted. While these statements are true the fact of greatest importance in the clinical interpretation of nail disease is that the nail behaves as if it grew from a line about 7 or 8 mm. proximal to the distal edge of the lunula. It slips distally over the dorsum of the phalanx somewhat as a hair pushes outward past the walls of its follicles. Nails grow at the rate of about 1 mm. per week. When one understands these things, comprehending the dynamic picture I attempt to give then interpretation is simple of nail plate manifestations of disorder

The Structure of the Adult Nail was described by Lewis (ADS 70 732 1954) as follows

"The 3 edges of the nail inserted into the soft tissue rest in a depression termed the nail fold (groove, sulcus, furrow)," Lewis wrote. "The skin extending from the fold over the nail is called the nail wall. The thin membrane extending from the proximal wall a short distance over the nail is the eponychium. The lunula is the convex lens-shaped whitish opacity which may be seen distal to the eponychium. The paronychium is that portion of the soft tissue surrounding the nail border whereas the perionychium consists of the paronychium plus the nail bed. The nail fold is divided into a dorsal roof and ventral floor by the nail root proximally and by the flanking borders of the nail laterally. The nail bed comprises all of the soft tissue immediately beneath the nail plate (body). The distal portion of the nail is subtended by a mass of keratin the hyponychium. The anterior (distal) limiting furrow is a crescent-shaped depression in the dorsal surface of the digit immediately distal to the hyponychium.

"THE MATURE NAIL.—The nail unit, in general, consists of closely united but poorly defined lamellae. Each lamella is composed of one or more layers of flattened epithelial cells forming scales or plates.

"The dorsal nail in the adult digit [takes] origin from up to one sixth of the proximal portion of the floor of the nail fold and up to one-half of the proximal portion of the roof of the fold. The mechanism of onychogenesis is that of the inflation deflation cycle described in the section on the term fetus. The basophilic dorsal nail is frequently retained in an irregular 'patchwork' manner to the free edge of the nail but may disappear before this distal margin is reached. *Lagermalm et al.* (*Nature* 168 1080 1951) in studying the skin and nail with the electron microscope found evidence of an epicuticle. That found on the nail was more contaminated by extraneous material than that from the skin. The thickness of the membrane was estimated by palladium shadow technique to be 100 A. units.

"Transverse section stained with silver protein demonstrate that in general there have been less flattening and amalgamation of cells in the dorsal nail than in the intermediate nail. The continuity of the corneous material in the lateral nail fold with that in the dorsal nail raises the possibility of onychogenesis in this region.

As in the fetus, the thickness ratio of the dorsal nail to the intermediate nail in the central portion of the nail unit compares grossly in magnitude with that of the thickness ratio of the glabrous epidermis to the dermis.

"The intermediate nail, or main nail body takes origin from the epidermis of the nail bed bounded by the distal margin of the lunula and the most proximal portion of the floor of the nail fold. [It] appears to originate from its *generative epidermis* by the process previously described as gradient parakeratosis. There is a change from the eosinophilic hue of the epidermal cell to a colorless or even palely basophilic appearance The nuclei tend to become smaller and if retained in the intermediate nail generally collect eosinophilic perinuclear material. Thus, phenomena may be found in the intermediate nail first, there may be horizontal streaking from flattened cell bodies or cell membranes, and second, persistent retained parakeratotic shrunken nuclei with perinuclear *eosinophilic material or acuolization. These latter elements might well be termed* 'pertinax bodies' from the Latin referring to their persistence in otherwise monotonous nail. The bodies are generally found in a galaxy longitudinally disposed from the middle of the proximal nail fold to the distal margin of the roseate nail bed. The pertinax bodies tend to maintain the same depth throughout the length of the nail, suggesting that pathology of the roseate nail bed will not be reflected at the nail surface

"The conversion to nail from the gradient parakeratotic area may be very abrupt. This type of onychogenesis may be found occasionally but to a lesser degree in other areas of the nail bed.

"The common border between dorsal and intermediate nails is rich in polysaccharide as demonstrated by the periodic acid Schiff technique There is usually some intermingling of nail layers at the common boundary The stain technic which most strikingly delineates the intermediate nail is that employing silver protein modified after Bodi

and Moskowitz. This stains the intermediate nail a striking yellow brown and [stains] the dorsal and ventral nails shades of blue-black. The ventral nail may show that of red and brown. This technique also best demonstrates the cellular pattern of the nail lamellae.

"The site of origin and the form of the ventral nail follow the description as given in the section on the term fetus. The ventral nail generative process suggests that of the dorsal nail inflation-deflation cycle. At its proximal limits, ventral nail generation appears to be limited to the epidermal ribs [which are] the longitudinal elevations in the nail bed distal to the lunula. The thickness of the ventral nail is [about] that of the dorsal nail however it may reach a maximum of one-third of the thickness of the intermediate nail. The ventral nail may be absent.

"The common border between the intermediate and ventral nails is rich in polysaccharide although less so than that between the dorsal and intermediate nails.

"It must be emphasized that separate and distinct dorsal intermediate and ventral nail layers cannot be demonstrated in every specimen and that the contrast is more striking in toenails than in fingernails.

"The hyponychium develops in a manner corresponding to that of the glabrous stratum corneum but contains many more eosinophilic vacuolated cells. These cells suggest their fetal predecessors, the large vesicular cells of the dorsal plume. These cells, present in both the fingers and the toes, are not stained preferentially by the periodic acid Schiff technique. The evolution of the dorsal plume into the hyponychium may be followed in the study of sections from fetal and mature digits. Many specimens reveal mechanical separation between the nail unit and the hyponychium as a result of sectioning. In these instances, the hyponychium is retained in immediate apposition to the epidermis of the distal prominence.

"Sandwiched between the dorsal nail and the distal portion of the eponychium may be found a stratified cornified plate which could be well termed the nail vest. It frays and disappears *shortly after its emergence from* the nail fold. This organ is pushed proximally with the eponychium during manicuring. The nail vest appears to arise entirely free from the roof of the nail fold. Portions of the vest may remain adherent to the surface of the dorsal nail for varying distances beyond the eponychium. The vest is also found in the lateral nail folds and here may extend medially onto the exposed nail.

"The dorsal surface of the nail bed epidermis presents longitudinal ribbing, which fits into corresponding furrows in the ventral surface of the nail unit. In the generative area of the intermediate nail the ribbing is much less promine t and may be absent. The epidermis of the nail bed distal to the lunula shows little to no ge erative acti it and this fo the most part is restricted to the ribs. There seem to be a gradual change ever from a sluggish gradient parakeratosis to onychogenesis in the presence of keratoh alin like granulation. The epidermis at the base of the hyponychium, the distal prominence of the fetus, frequently distinguishes itself by presenting vacuolization of its cells. The promi ence i greatly flattened be eath the mature nail. The majority of the basal cells of the medial two-thirds of the nail bed epidermis from the region of *the distal margin* f the lunula to the generative area of the ventral nail may lose both nuclei and cytoplasm but retain their original cylindric contour with the long axis perpendicular t the basement membrane. Laterally the basal cells resemble those of the glabrou skin. Progressively distad serial sections show that, in the generati e epidermis of the ventral n il, the basal cells may show nuclei and, further distad, [may show] nuclei and cytoplasm. This alteration is noted in fetal specimens as early as the third month.

"Rete ridges are an anatomic feature of the epidermis of the floor a d lateral ... the f the proximal nail fold. The ridges are markedly increased in length di tal t the lun la.

"The dermis of the nail bed and nail wall is arranged in dorsall elevated waves reflecting the longit dinally disposed epidermal ribs. Heretofore these wa es ha e been ref rred to incorrectly as papillae they might well be named dermal ribs. Elastic tissue in the dermis generally runs parallel to the long axis of the *finger; in the dermal ribs* ... *the* last fibers run vertically In contrast with the fairl orderl patt rn of the ... tissu the ret culum fibers are seen in sections stained by the M llory phosphot ... tech ie to ru in a helt r-skelter manner occasionally a vertical preference ... the nail bed derm and a horizontal preference in the nail-fold dermis. ... may be found in the nail bed, especially beneath the proximal nail fold, ... thro ghout three fourths of th depth of the dermis.

It of interest that as early as the third mo th of f tal life keratl ... arranged lam line of flattened c lls, seen to evolve into the future m t re nail, ... At this stage observed to be d elopi g from both the roof and the floor of the nail fold. ... further invagination of the fold is till taking place. The epo ychium shares in the ... genic acti ty at this state At 5 m ths, the future dorsal nd intermediate ... quently be d ffere tiated; the ve tral nail, when present m kes its appearance ... *before term.*

"The mature nail unit may be shown by serial section with selected stains, ... silv r prot in, to be made p f 3 components, namely dorsal, i termediat and ventral. ... silver protein-stain technique surprisingly enough demonstrated the greatest ... detail in the flattened cells of the nail substance The opacity of the ...

thought] a result of keratohyaline granulation [but] in general, this area is free from keratohyalin like granulation. If granulation is present, it is [here] in minimal concentration [but] is heaviest in the epidermis of the roof of the nail fold and generative areas of the ventral nail hyponychium.

Senile Changes in the Nails were discussed by Lewis and Montgomery (JID 24 11, 1955) The alterations of the aging process include dullness, opacity increased longitudinal ridging changes of color alterations of thickness and masking of the lunula. The authors investigated the concomitant histologic features.





Fig. 1846.—Thin nails with longitudinal striae in man with macrocytic anemia.
Fig. 1847.—Subungual hemorrhages, longitudinally following the nail bed ribs, symptomatic in Raynaud's disease. (Dr F Ronchese.)



Fig. 1848.—Clubbed fingers, in a case of bronchiectasis. (Wiener Skin Manifestations of Internal Disorders, Mosby 1947.)

Systemic Disease, which, say for 1 week damages the nutrition of the entire growing zone of all 20 nails, will result in the appearance on each nail plate of a transverse line convex distally visible as soon as the nail has grown out far enough to be seen beyond the proximal nail fold and every nail will be similarly affected. The width of the line must be about 1 mm., malnutrition having lasted a week by hypothesis. Looking at a series of Bean's lines, as such transverse bands are called one readily estimates—on the basis of 1 mm. per week as the rate of growth—how long ago it was that the damage occurred.

Local Disease, if it alters nail nutrition by causing inflammation of the terminal phalanx of the digit must similarly leave its mark on that nail. Contact dermatitis and acrodermatitis so mark the nails.

Evanescent Disorders damaging the growing zone at scattered points over a period of time register themselves on the nail plate as a scattering of thin, pitted spots. Following a shower of miliary injuries, of systemic origin but



Fig. 1849.—Transverse marks on some nails, not all, denoting previously active dermatitis of the phalanges



Fig. 1850.—"Depressions transversales en fosse" for which in this instance no cause could be discovered by Dr. F. Ronchese. Several marks are contemporary as judged by their distances from the nail roots, suggesting a systemic origin.



Fig. 1851.—Transverse bands, caused by severe seasickness

fortuitous in their terminal disposition, pits may range across the plate in an arc. The duration of the period during which this occurred is commensurate with the sagittal length of the involved portion of the nail plate

TRANSVERSE BANDS of all nails signify temporary damage of all nails, which implies systemic causation Transverse bands of isolated nails signify temporary damage of the affected nails as a result of local disturbances, which might of course be the local accidents of systemic disease.



Fig. 1352.—Transverse bands due to acute pellagra 4 months previously (Dr W C Brownson.)





Fig 1353.—Transverse pigmented stripes due to stimulation of melanocytes by x-ray therapy given 6 weeks previously (Sutton J 150 210, 1952.)

Fig. 1354.—Transverse bands occurring in the course of Hodgkin's disease. (Dr F Ronchese)

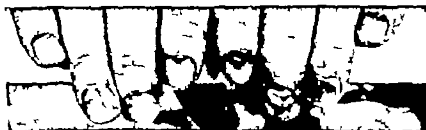


Fig 1355 —Beau' phenomenon occurring in a patient with pemphigus vulgaris whose palliation with cortisone induced normal regrowth.

Transverse arcuate zones of altered nail substance are called Beau s lines. They are due to sudden arrest of the function of the matrix, which may be more or less prolonged, and which results in the cessation of production of normal matrix cells. This causes the formation of a hiatus in the continuity of the nail plate When etiologic factors act repeatedly multiple Beau s lines result (Pardo-Castello)

I have seen them following seasickness. The 2 cases of Simons (NederlTijdGeneesk 81 1918, 1937) followed arsenical intoxication; the lines were zonal leukonychia, rather than zonal atrophy and representative therefore of a slighter *degree of injury* than that which causes actual atrophy. The bands in the patient of Cornala (ADS 38: 412, 1938) dated the roseola of syphilis. They can *follow* any general intoxication and mark the history of a metabolic stat (Wirtschafter and Littman: ADS 42: 874 1940). Pellagra was the cause in cases seen by Brawnson (SouthMJ 8: 672, *1915*) a fract red hip in that of Zeisler (ADS 36: 231 1937), exfoliative dermatitis from gold in that of Bellafante (NederlTijdGeneesk 81 2613 1937), cardiac infarction with associated malnutrition during a desperate sect in that of Urbach (ADS 5..: 108, *1948*). Transverse bands of melanin hyperpigmentation have been seen following x ray therapy. Jones I (J 150: 210 195..) reported a case; a dozen others have been brought to my attention by widely scattered observers, including Dr Yandell and similar pigmented bands were *seen following* the administration of ACTH and cortisone to a Negro (Thorn et al. NEngJM ... *782 1950*)

The nail structure was altered through its full thickness *in the cases* of transverse band atrophy of the *plate* studied histologically by Alkiewicz (*AnndeD* 6: 3.. 1935). Thinning, alteration of color and weakness of union were noted, and the abnormality showed an oblique passage through the *plate if the* section was longitudinal, the abnormal undergrowing the normal as it pushed distad.



Fig. 1356.—Permanent nail root alteration by subungual fibroma, producing longitudinal defect. (Dr O G. Costa.)

Fig. 1357.—Longitudinal striae due to radiation atrophy from use of fluoroscope.

Fig. 1358.—Longitudinal pigmented stripe presumably due t nail root junction nevus (Dr O G. Costa.)



Fig. 1359.—Longitudinal striation of nails in Darier' disease

Shedding of the Nails is the maximum defect of the Beau's line sort. Regrowth usually occurs. Shedding as distinguished from avulsion and onycholysis, means simply that the nutritional disturbance was grave and fairly enduring. Shedding of the nails is a common sequel of scarlet fever and it may occur in the course of other severe maladies such as typhoid fever, pemphigus and exfoliative dermatitis.

Enduring Disorders of the growing zone may be produced by malformation, roentgen or arsenical damage, or the presence of a nevus or a cicatrix. The result is that a fraction or all of the growing zone is enduringly or even permanently different from the remainder. The nail substance growing forth from it is different; the nail plate must register a longitudinal stripe.

Longitudinal Lines must signify enduring alteration of the growth zone of the affected nails. If a systemic disorder, perhaps nutritional, persists for from 4 to 6 months, that is long enough for longitudinal lines to progress through the length of all 20 nail plates. Congenital defect is a possible cause

Longitudinal stripes originate not invariably in the root but sometimes represent the longitudinal proximad extension of onychomycosis (q v) Monilial as well as trichophyton infection may produce them. Mycotic longitudinal striae do not ordinarily extend proximally under the proximal nail fold, and they are likely to be wider at the distal margin. Splinter hemorrhages (q v) are disposed longitudinally the explanation for this disposition being anatomical.

When the 10 fingernails show longitudinal lines, and the toenails do not, the cause is likely to be x ray injury such as affects the hands of physicians using the fluoroscope carelessly When all 20 nails show such lines, the cause is likely to be arsenic iron deficiency or macrocytic anemia.

Mees (NederlT jdGeneesk 80: 312, 1936) found ungual striae in cases of arsenical polyneuritis, and these contained 6 times as great concentration of arsenic as the rest of the nail. Simons (NederlTljdGeneesk 81: 1913, 1937) described 2 cases of transverse, leukonychial, arsenical bands. Avitaminosis may produce both transverse depressions and longitudinal striae, according to White (J 102: 2178, 1934)

Pigmentary stripes, apparently due to the presence of benign melanoma i the matrix, were recorded by Montgomery (JCutD 35: 99, 1917), Templeton (ADS 14 533, 1946) Schoch (Dermatologia 97: 123, 1948) and others. When the terminal phalanx of a young man was amputated because of this abnormality a benign junction nevus was found reported Koble et al. (ADS 65: 49 1952)

Verruca vulgaris involving the proximal nail fold may cause longitudinal striation, and so may lesions of lichen planus (Vero ADS 26: 677, 1932) A synovial cyst was the cause in the patient of Anderson (ADS 55 828, 1947) Roentgen keratosis is a cause of striae as well as of pterygium. Mycotic infection f the nail often grows proximad to form a stripe (Young: ADS 30: 186, 1934) Frohn (DZtschr 74: 136, 1936) described 10 cases of leukonychia striata, many cases of which are traumatic in origin. Longitudinal striae affected all nails of the man reported by Ochs (JCutD 32: 234, 1914) and had been present since birth.

Basic Types of Nail Diseases can readily be put in an orderly form by considering the systemic and local agencies that interfere with normalcy of the nails, in combination with their evanescent or enduring time of action upon the nails (1) enduring systemic disease may be expected to cause longitudinal lines in all nails, such as might accompany arsenical keratoses (2) transitory systemic disease may be expected to cause Beau s lines on all nails (3) enduring local disease may be expected to produce longitudinal defects of particular nails such as the pigmented stripe due to a nevus cell tumor located in growth zone tissue and (4) transitory local disease may be expected to cause temporary defects of various degrees, basically transverse in their disposition in the plate growing out with the remainder of the plate as the growth zone resumes its normal function A systemic disease by its local accident may damage nails fortuitously as in lichen planus or psoriasis, and the damaging influence may act for various periods of time.

When a nail is invaded by a fungus which enters it from the margin distally or laterally the situation is complicated by the existence of 2 independent rates of progress the rate at which the nail grows distad and the rate at which the fungus invades proximad. The balance between these 2 rates is of prime importance to the patient, for if circumstances can be so arranged that the outward rate of nail growth exceeds the invasive rate of the fungus, the patient eventually gets well.

Etiological Classification of Diseases of the Nails may likewise be undertaken in the effort to be systematic. Nails are influenced by

MALFORMATION as in congenital ectodermal defect of one sort or another including pachyonychia.

NEOPLASIA, such as melanoma carcinoma or subungual exostosis.

TRAUMATIC, PHYSICAL, MECHANICAL, AND CHEMICAL INJURIES of various sorts, which may loosen the plate from its bed, as a blister loosens the epidermis from the deeper layers. A bruise may cause hemorrhage beneath the plate and so generally loosens it from its bed. Hemorrhage manifests itself as a bluish purple petechia variable in its effect on the growth of the plate in

accordance with its location with regard to the growing zone. Physical factors of the environment affect the nails, such as low humidity in winter which leads to brittleness of the nails. Nails are loosened from their beds by exposure to excessively hot water—people differ in their vulnerability to this kind of trouble—and by exposure to alkali or acid, and by the habitual trauma of occupationally picking at something. Mechanical distortion of the toes by tight and ill fitting shoes is the commonplace cause of forcing soft tissues into the path of the growing nail so that ingrowing nail results.

METABOLIC ALTERATION of the bodily economy. In avitaminosis nails suffer along with other epidermal structures. In hyperthyroidism, they are likely to be thin and fragile. In hypothyroidism onycholysis is often seen. In the Plummer Vinson syndrome koilonychia is a typical symptom.

INFLAMMATORY ALTERATION WITH LOCAL ACCIDENTS to the nails as in syphilis, leprosy lichen planus psoriasis pemphigus scleroderma, dermatitis venenata, eczema, pustular acrodermatitis, infectious eczematoid dermatitis, keratoderma gonorrheica, and granuloma pyogenicum (all of which are described in other chapters). These influence the nail through their incidental alteration of local tissues. Diseases of the nails and dermatoses of the digits are really separate subjects, for nail diseases proper are those which are peculiar to the nail itself, while digital disease comprises almost the totality of dermatology.

Thus parasitic inflammatory affections fall into 2 classes: (1) parasitism primarily affecting the adjacent soft tissues, such as infection with the virus of verruca vulgaris, with staphylococci, streptococci, or bacilli, such as that of anthrax, with spirochetes such as that of syphilis, with fungi, such as those of tinea and moniliasis, and with animals, such as *Sarcopsylla penetrans*; and (2) parasitism of the nail plate, the substance of which is chemically the same for practical purposes, as the corneum, is a suitable culture medium for many of the Fungi imperfecti, which grow into it from its free margin. If the proximad progress of the growth of the fungi exceeds the rate of distal growth of the nail plate inevitably the nail becomes more and more extensively involved and damaged until, as in *Trichophyton purpureum* infection (q v), there may remain only a crusted flaky mass of distorted material extending actually underneath the proximal fold and supplanting the entirety of the nail plate. The infected nail is an important focus of mycotic infection. See Onychomycosis and Mycotic paronychia.

NEUROTIC HABITS.—Onychophagia, onychotillomania and perhaps attrition through scratching may be included here.

COMBINATIONS OF FACTORS.—Nails may be malformed, malnourished, traumatized, scarred, infected or neglected in any combination.

Prognosis.—A nail capable of growing is able to replace itself in about 4 months. The outlook for ultimate replacement therefore depends on whether the growth zone is permanently altered and whether the locally damaging influences can be remedied. Damage to the plate distal to the growth zone is temporary, for the structures are replaced. Traumatic separation of the plate from its bed, accidental or purposeful, heals in due time with a noteworthy lack of distortion. Malformations are irremediable except by the radical correctional revisions of plastic surgery. But systemic diseases can often be treated with success. Mechanical troubles are usually easy to correct. Scars do not lend themselves to therapeutic alteration save by excision and the substitution of a perhaps better scar. Local inflammation requires its individual interpretation and prognostic assay. Melanoma of the nail bed is highly malignant and requires amputation.

Treatment of Nail Diseases. Generalities.—One attacks the underlying cause if possible. Nutritional deficiencies, hypothyroidism and infections, such as syphilis, are responsive. Onychomycosis and mycotic paronychia have been discussed. Mechanical lesions such as those due to manicuring are easily altered. Local injuries, inflammatory manifestations and inflammatory diseases must be attacked in accordance with dermatologic principles just as they would be if the trouble were located elsewhere. One should promptly perforate the nail plate to let out blood or pus from beneath it.

After injecting procaine deep into each side of the proximal phalanx for obtaining local anesthesia, one may freely cut across a nail plate and tear off the distal portion; regrowth and healing take place in due time. One may destroy the epithelium of the nail bed by the superficial blistering application of the cautery after removing the plate distal to the growing zone and healing and regrowth under simple greasy dressings take place almost painlessly and with little permanent distortion. Severe verrucous paronychia and rare subungual verrucae are thus treated effectually

It is necessary not to mistake pyogenic paronychia for ingrowing nail and so to perform one of the various plastic operations on soft tissues designed to pull them away from the direction of nail growth. Neoplasia demands surgery Finger pulp infections, felons, I likewise refer to surgeons, along with other infections of the hand. A furuncle in a digital hair follicle is *not* correctly treated by extracting the hair this procedure is likely to result in a subcutaneous abscess.

Nail nippers and an electric drill such as the Craftsman hand instrument or a dental device are essential instruments in treating nail conditions. Their use and also the technic of avulsion, are described in the discussion of Onychomycosis, q v

GENERAL REFERENCES ON DISEASES OF THE NAILS.—See also Anatomy nails; Embryology nails; Dermatitis venenata, cosmetic and occupational; Dermatitis medicamentosa, quinacrine; Syphilis, primary Tinea, mycotic paronychia and onychomycosis Dermatitis of the hands and feet; Scleroderma; Raynaud's phenomenon Congenital ectodermal defect, Pachyonychia; Subungual exostosis Glomus tumor; Melanoma. See Jackson (JCutD 23: 151, 1905) various cases Heller (Krankheiten der Nagel, HandbHwG, Springer 13 2: 1-423, 1927); Monash (ADS 25: 876, 1932), normal pigmentation of nails in Negro; Cockayne (Inherited Abnormalities of the Skin and its Appendages, Oxford U Press, 1933, p. 260, ff.); Whitehead (PaMJ 40 280, 1937) nail changes in common skin diseases; O'Donovan (Pract 141: 177, 1938) generalities; Lamb (JOklaMA 31: 39 1938) general discussion; Clark and Buxton (BJD 50: 221, 1938), growth rate measurements, 3 mm./mo. Low (Pract 142 627, 1939), nail changes as aids to diagnosis; Pardo-Castello (Diseases of the Nails, Thomas, 1941, 183 pp.) valuable monograph; Goodman (UCutRev 45 692, 1940) manner of growth and influence on nails of disease processes; Sagher (JID 11: 337, 1948) histology of onychomycosis, Ronchese (ADS 63: 565, 1951) various nail diseases; White and Laipply (JID 19: 121, 1952) histopathology of 44 various cases Ronchese (IndustMed 22 245, 1953) occupational marks on nails.

MALFORMATION OF THE NAILS

Anonychia is total absence of nails, an extraordinary congenital anomaly Rarely in a patient born with nails the nails are shed and do not grow back. Pardo-Castello (1936) reviewed 3 cases. Hutchinson (ArchSurg 1891 p 237) saw 1 associated with alopecia as a congenital defect. Anonychia of the thumbs only was a dominant character in a family reported by Ebstein (D Wehn 68 113 1919) Defective nails associated by heredity with defective patellae have been recorded (Osterreicher WienklinWehn 1: 632, 1929 Senturia and Senturia: JRoentg 51 352, 1944)

Three forms of anonychia were described by Alkiewicz (AIDuS 178: 224, 1938): aplastic, atrophic and hyperkeratotic. The aplastic form depends on congenital absence of the nail growth zone; there is no nail. One finds the lateral nail folds absent, and the dorsum f th terminal phalanx is thin and red. The atrophic form represents the nail changes of any process leading to atrophy of the epidermis when the nail is involved thereby In "anonychia keratodes," the hyperkeratotic form, there is usually a dome-shaped, horny mass of loosely coherent keratin, surrounded by thickened skin which allow the defective nail to lie in a groove whence it grows vertically its superficial layers being easily detached by scratching While the disorder is usually congenital, it may be caused also by pathologic processes which destroy the nail-forming tissues. The nail base i replaced by acanthotic, laminated, flat epithelium productive of the loose keratin.

Absence of a nail results in lack of normal support for the pulp and reduces the usefulness of th finger tip, diminishing the fine qual ties of tactile appreciation. Transplantation of nail from toe to finger was accomplished with notable success by McCash (BMJ 1: 893, 1955)

Displacement (Heterotopy) of the nails has been seen. Gigantism of a nail may occur in Recklinghausen's overgrowth of a digit.

Pachyonychia Congenita.—See p. 1047

Atrophy of the Nails (Onychatrophia Atrophia Unguium) is characterized by changes which may affect the consistency elasticity shape, size or con

Fig. 1860.—Supernumerary nail on thumb. (Dr F Ronchese.)
Fig. 1861.—Congenital deformity with one nail on the one digit. (Dr Robert X Andrade.)
Fig. 1862.—Median canaliform dystrophy. (Robinson and Weidman: ADS 87: 122, 1941)



Fig. 1863.—Polydactylia: rudimentary supernumerary finger presenting as [illegible] artilike tumor of the hand. (Hare: BJD 66: 402, 1954.)

tour of the affected plates. As a rule they are thin small, opaque and lusterless, and longitudinal or transverse grooving is common. Occasionally the surface may be marked by pits or depressions, which impart to the nail a rough, worm-eaten appearance.



Fig. 1844.—Congenital micronychia. (Drs. J. C. D. King and H. G. Parker.)



Fig. 1845A.—Congenital atrophy of nails.

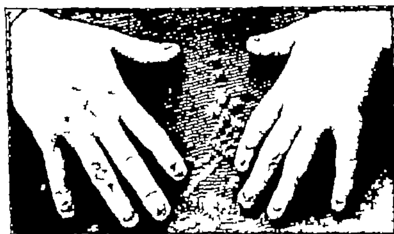


Fig. 1845B.—Epidermolysis bullosa, showing atrophy of nails.

Hydrolyzed wool, furnishing sulfur when given by mouth, seemed to help the cases of Klauder and Brown (ADS 31 26 1935) wherein congenital dystrophy was associated with abnormally low sulfur content of the nails.

Congenital Atrophy when associated with alopecia (q. v.) may show both atrophic and hypertrophic changes, as in the hereditary cases reported by White (JCutDis 14 220, 1896), Nicolle and Halpré (AnndeD 6, 676, 804, 1893) and Hardwick (BJD 51 4 1939). In the congenital alopecia syndrome with pachyonychia (q. v.) the nails are usually narrow, laterally curved and lifted from the bed distally with dark, horny masses of keratin (Sequeira BJD 4 122, 1912). Lane (AnndeD May 1924) described an otherwise healthy family in



Fig 1866.—Pachyonychia congenita with keratosis palmaris. (Dr Robert N [illegible])

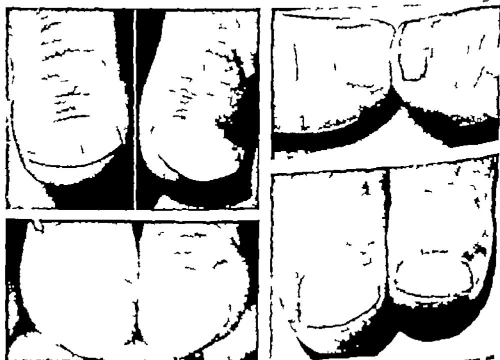


Fig. 1867.—Racket nails, bilateral, are depicted on the left. Unilateral racket nail is seen on the right. (Ronchese ADS 63: 565, 1951)

which congenital atrophy of the nails occurred in all of the females, and Tobias (J 84: 1563, 1925) another family group in which there were 12 well-defined cases of dystrophy of the nails in 4 generations. Waite and Bradford (JMoMA 25: 30 1928) found that more than 30% of the members of th family showed congenital atrophy of the fingernails; the defect appeared to be transmitted principally through the female.

Nail en Raquette, a dystrophy of wideness especially of the thumbnail, is associated with diminution in transverse curvature. According to Ronchese (ADS 63 565 1951) this rare anomaly has been thought a minor sign of congenital syphilis (Bois AnndeD 7 415 1926) It may be unilateral or bilateral, and may or may not appear in other members of the family In the 63 cases investigated by Ronchese it did not appear in the toenails, and it affected females predominantly It would seem to have no significance.

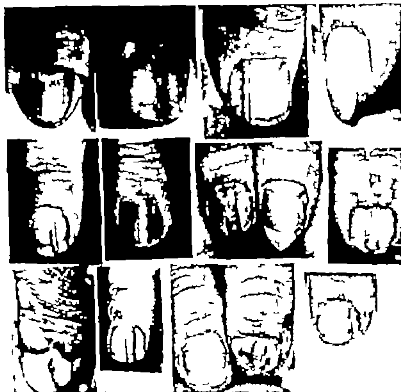


Fig 1388.—Longitudinal groov dystrophia mediana canaliformis. (Dr F Ronchese)

Median Canaliform Dystrophy is manifested by a curious longitudinal streak in which the nail is folded in a narrow radius so as to form a slender cylinder (Heller: DZtschr 51 416, 1928) Extending from the root to the free edge where the nail becomes fissured, this rare anomalous condition has something to do with parakeratosis (Robinson and Weidman ADS 57: 328, 1948) The streak is discolored, and most of the few reported cases have affected the thumbnails.

The nails of the thumbs and fifth fingers began to develop longitudinal atrophic striae representative of this type of dystrophy at age 6 in the girl presented by Oliver and Bluefarb (ADS 49 190 1944) Compare longitudinal fissures. The abnormality grew out and re-formed repeatedly in the case of Sweet (ADS 64: 61 1951) Whether the disorder is nevoid or traumatic in origin was discussed in the presentation of 2 cases by Cole and Driver (ADS 52: 418 1945) Costa (ADS 47: 406 1943) reported a case and reviewed the literature briefly

X ray therapy was said to have been curative in a case of Ledo (AnndeD 10 765 1929) The disorder of recent onset in a young man disappeared after the extraction of 3 abscessed teeth in the case of Fowle and Wiggall (ADS 50 267 1944)

NEOPLASIA AFFECTING THE NAILS

See Adenoma sebaceum, with its subungual lesions Melanoma, melanotic whitlow, Glomus tumor Subungual exostosis and Squamous carcinoma, nail bed primary

Pigmented Nevi have been noted causing longitudinal pigmentary striation (q v) Rarely they occur in the nail bed. Benign pigmented intraepidermal nevus was discussed by Traub (ADS 61 1025 1950) who believed that 1 of the cases reported by Bloch (AfDuS 153 20 1927) as benign non nevoid melanoepithelioma was in fact a junction nevus. It would seem that either junction nevi or superficially located macular blue nevi (q v) may lie under or adjacent to a nail.

INGROWING NAIL (UNGUIS INCARNATUS)

The lateral border or distal edge of the nail may grow into the soft tissues. Tight shoes are the common cause, for they force the soft tissues of the lateral fold particularly at the end of the great toe, into the direction of growth of the nail. To trim across the nail cutting under the fold, is an error which makes the disturbance likely to occur Often in so cutting the nail the lateral edge is not quite reached by the cut and a sharp spike at the edge invisible because of its location under the fold, grows forward into the flesh Such a lesion is exquisitely sensitive to pressure over the spike. Secondary infection is to be expected.

PREVENTION is preferable to treatment wear shoes of ample spaciousness and trim the distal edge of the nail transversely so that its lateral margins lie beyond the distal part of the nail fold, rendering imprisonment of the nail impossible

TREATMENT —One may repeatedly shove cotton under the nail at the edge until the nail grows beyond the end of the toe. One may cut away the nail and pull it from the cavity but recurrence is likely One may split the nail longitudinally near the lateral fold and excise the fold itself and the proximal growth zone tissue so that that part of the nail is permanently amputated (Kirschenmann AmJSurg 36 349 1937) Heifetz (AmJSurg 38 298 1937) cut out only the nail and its matrix, leaving the soft tissues untouched. One may scrape the central longitudinal zone of the nail so thin that the plate will bend on this as a hinge then, lifting the ingrown edge from the sulcus, one puts pledgets beneath it without cutting off the spur until it has grown out (Chapman BMJ 2 1073 1934) One may cut or burn away the lateral fold, so altering it plastically that recurrence of impacted nail (Marton I Cut Rev 41 253 1937) does not occur Bartlett (J 108 1257 1937) excised a longitudinal lunate wedge of skin from beside the nail so that when the wound was stitched together soft tissues of the lateral nail fold were pulled away from the border of the nail. Linch (SouthSurg 8 173 1939) devised a splint to evert a nail from its lateral sulci. Manson (USNMBull 41 1090 1946) removed the lateral third of the nail plate and matrix without removing soft tissue

Methods for removing a nail entirely and permanently which is hard to do were discussed by Nuttall (Lancet 2 100 1941)

SYMPTOMATIC DISORDERS OF THE NAILS

Trauma.— A crushing injury such as the blow of a hammer is likely to cause subungual hemorrhage At first red, the extravasated hemoglobin is transformed as it is in an ordinary bruise becoming black. If the blood blister occurs within the growing zone, the nail is shed partially or completely and

regrowth eventually occurs. An injury which cuts through the growing zone and scars it leads to the development of a permanent longitudinal stripe. It is difficult to succeed by surgery in destroying the entirety of the growing zone usually there remains enough of it to produce little, twisted horny spikes which persist in the scar

SUBUNGUAL BLISTERS AND PURULENT BLEBS.—The analogues of friction blisters of the skin may form under the nails under suitable mechanical conditions. Persons afflicted with congenital ectodermal defect or epidermolysis bullosa are particularly susceptible. Long toenails and short shoes predispose to this, and I have seen it occur in patients with occlusive peripheral vascular disease who had diminished sensibility of the toes so that they were not aware of injuring themselves.

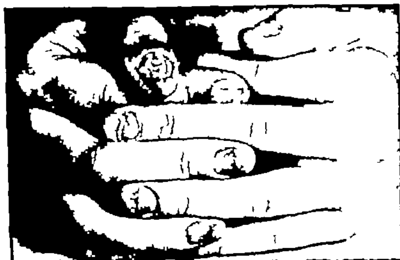


Fig. 1369.—Occupational nail changes in a bakery employee, due t handling sugar (Dr Clyde L. Cummer)



Fig. 1370.—Damage of nails, due to handling photographic chemicals.

Dissolutions of adherence between nail plate and bed are liable to infection with pyogenic organisms, as other blisters are. The subungual purulent bleb which results is exceedingly painful until an adequate window is cut in the overlying already separated nail plate to let out the exudate. A cautery may be used (Saunders ADS 56 269 1947) or a red-hot paper clip (Willcock BMJ 2 683 1952) to make a hole in the nail painlessly One should flush the cavity and dress the lesion with an antibiotic ointment, such as tetracycline which might well be given by mouth also.

A friction blister at the side of the nail separates the epithelium of the lateral fold as well as that of the matrix from the underlying connective tissue. Becoming infected, there results a common type of purulent paronychia with

subungual extension. One should cut away the overlying nail plate pull it from under the fold take away the cap of the *bleb* and apply suitable antiseptics and soaks or wet dressings until healing by epithelization is complete.

USURE DES ONGLES is the French designation for the attrition, terminal curvature and polishing of the nails which occurs as a symptom of widespread pruritus and the *scratching* so occasioned Its existence *tells the practitioner* at once that the *patient is a* long-suffering one Occupational attrition, as well as traumatic and pruriginous, *may* be included in the term.

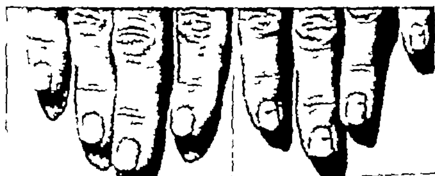


Fig. 1871.—Onycholysis, cause undetermined. (Dr John Shahan)

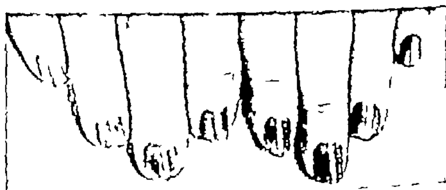


Fig 1872.—Onycholysis and subungual hyperkeratosis caused by nail lacquer undercoat (Winston and Sutton JKansMS 49: 371, 1948)



Fig 1873.—Shedding of nails. (Case of Sutton, Sr noted in text.)

OCCUPATIONAL AND CHEMICAL ATTRITION of the nail plate can take place Erosion of the distal portion such as affects occasional photographers may or may not be subjectively symptomatic Exposure to hot alkaline maceration will separate *the plate* from the bed more readily in some persons than in others, and paint removers and strong detergents can do this see Onycholysis, and Dermatitis venenata occupational. Onychia due to sugar handling was noted by Cummer (ADS 41 142 1940) and changes associated with exposure *to gasoline or KOH* by Alkiewicz (AnndeD 10 136 1950) Fur fleshers are

liable to the affection (Heimann and Silverberg ADS 44 426 1941) The article of Templeton (J 97 1950 1931) was devoted to onycholysis as an occupational disease.

Onycholysis is a term applied to loosening of the nail from its bed not as a result of growth zone failure, primarily In the cases of Templeton (J 97 1950 1931) the disorder regularly began with brownish spots under the distal border of the nail and asymptomatic shedding occurred within a few days, when certain patients immersed their hands in water When not traumatic, or due to hot water alkali or occupation, as in a patient of Viecelli (ADS 33 697 1936) [compare traumatic occupational and chemical dissolution] the condition may be idiopathic, but it is usually symptomatic of nail matrix disturbance such as may occur in psoriasis eczema, hypoproteinemia or syphilis. Trauma, such as that occasioned by short shoes and athletic enterprise may aseptically blister the great toenails, or other nails, especially if they are trimmed long Freed from its bed, the nail is not normally translucent but it grows in normally in due time Low BMR and improvement with thyroid were observed in a number of cases by Fox (ADS 41 98 1940) Both hypothyroidism and occupational factors of mechanical and chemical sorts were together etiologic in the case of McRoberts (NoWMed 39 95 1940)

Onycholysis due to nail undercoats was thought to represent chemical dissolution, not allergy by Winston and Sutton (JKansMS 49 371 1948) see Dermatitis venenata cosmetic. The use of artificial nails attached by an adhesive caused this phenomenon, reported Frumess et al. (J 149 828 1952)

Onychomadesis (Onychoptosis) is an uncommon disorder characterized by periodic or intermittent shedding of 1 or more fingernails or toenails. The affection frequently involves only certain fingers or toes, usually without apparent cause. Montgomery (JCutD 15 374, 1897) described a case in which the tendency to nail loss appeared to be hereditary and more or less continuous. Shedding of the nails in such conditions as exfoliative dermatitis is not what is meant here. Brown-Séquard reported a case of onychoptosis which developed following section of the sciatic nerve and Sutton Sr noted a somewhat similar instance associated with a crushing injury of the leg following which the great toenail plate was thrown off regularly at intervals of about 9 months. Falcon (GazHôp 8: 156 1867) and Sutton, S have observed recurrent shedding of the nails preceded by tingling and suppuration of the matrix in hysterical persons. Freyberg et al. (J 107: 1769 1936) reported a hypoparathyroid woman 36 years old with shedding of the nails. A case was noted which involved all of the fingers each year when the man worked with leather gloves in his garden, perhaps as a result of mechanical influences and so deserving the name onycholysis rather than onychomadesis (J 110: 67 1938) Localized epidermolysis bullosa (q.v.) could also account for such phenomena. Disorder of the nails had its onset coincidentally with alopecia areata and the requirement for military service in the patient of Bloom (ADS 57: 631 1948)

Onychorrhexis (Brittleness of the Nails) may be congenital or acquired. It may be accompanied by longitudinal furrowing and the nail plates are usually more or less thinned. Low humidity nail polish and polish removers (acetone) and frequent washing with hot water and alkaline soaps are possible causative factors. In hypothyroidism the brittleness of the nails may be relieved by doses of thyroid extract. When the nails are thin and fragile as I see them more often in women than in men, I generally prescribe iron and often give estrogenic substances by mouth with good effect. Protein deficiency must also be considered; Tyson (JID 14: 323 1950) obtained benefit with the administration of gelatin. When gelatin was given to patients with brittle nails by Rosenberg and Oster (ConnSMJ 19 171 1955) some were helped, especially those with splitting of the nails, while others were not. I suspect that the hypoproteinemic ones improved and that the others needed iron, thyroid or estrogenic substances. See QMN (J 131: 1153, 1946); Cornbleet (ADS 62: 436 1950) histology

Fragilitas unguium was investigated by Silver and Chiego (JID 3: 25 1940) who reviewed the literature pertinent to the influences of avitaminosis, iron deficiency temperature humidity pH and solvents. Their effort to devise a measurement of fragility failed, but they were able to conclude that dehydration was more significant than defatting

A cream for brittle nails (QMN: J 111: 559 1938) may be prescribed

℞

Triethanolamine	2.0
White petrolatum	1.5
White wax	0.5
Anhydrous wool fat	0.5
Water	12.0

Koilonychia was the name suggested by Heller for what Crocker described as spoon nails (Wise JCutD 37 467 1919) This disorder usually affects the fingers only and it may be hereditary or acquired. The nails are thin and concave from side to side with the edges everted. Crocker's case developed in the course of an attack of lichen planus. Spoon nails have been seen in syphilis (Fox ADS 2 265 1920) acanthosis nigricans, cachexia, hypochromic





Fig. 1874.—Spoon nail. (Dr H. C. Varney)
Fig 1875—Split nail. (Dr F Ronchese.)



Fig 1876.—Pachyonychia and split nail. (Dr O. G. Costa.)



Fig 18 7—Onychauxis in a syphilitic patient. (Dr Irwin C. Sutton)

anemia (Witts GuysHospRpt 80 253 1930 Roesegger: MWelt 10 19 1936) hypothyroidism and Plummer Vinson syndrome (Anderson ... 816 1938) Cases associated with iron deficiency were reported by Clarke (NEngJM 227 338 1942) with thyrotoxicosis by Cooke and Lutz (BMJ ... 207 1944) with polycythemia by Glazebrooke (EdinMJ 51 65 1944) and with Banti's syndrome, treated by splenectomy and subsequently required gastrectomy by Rothman and Shapiro (ADS 58 499 1948)

Familial cases have been noted. Koilonychia was so extreme in the great toenails of some members of a family studied by Hellier (BJD 62 213 1950) that it interfered with walking.

EGGSHELL NAIL is a similar disorder characterized by upturning of the free border with increased translucence of the entire plate (Hyde JCutD 24 145 1906)

PLATYONYCHIA (FLAT NAILS) is an abortive form of koilonychia which may appear in members of a family for generations (Kartamischew DWehn 1936 p 1257) Rosegger (1936) stated that in addition to its usual familial occurrence it may be caused by immersing the hands in soapsuds oils creosote or coal tar Cirrhosis of the liver is frequently causative according to Kleeberg (Lancet 2: 248 1951)

Longitudinal Fissures (Split Nails) are annoying If the trauma causing the split destroys a portion of the growth zone little benefit may be expected from treatment of the scar Carter (J 90 1619 1928) described a method of drilling the plate and suturing the parts together MacLean (J 110 1775 1938) applied a solution of celluloid in amyl acetate, unbreakable watch crystals being particularly suitable sources of the solute. Alkiewicz and Gorny (AfDuS 175 467 1937) described the histology of longitudinal fissures, which they classed as partial or total and temporary or permanent. The gap in the area of epidermal nail formation was demonstrated. In the nail plate the fissure was a discontinuity in horn which was replaced with hyperkeratotic epidermis.

Onychauxis is the term applicable to hypertrophic overgrowth of the nail plate It may be congenital or acquired, idiopathic or symptomatic. Paronychia is a common complication. Hypertrophic nails are often brittle and friable sometimes splitting without apparent cause. Onychauxis may complicate any chronic scaly dermatitis, such as eczema or psoriasis, and it may result from a variety of dermatoses, including keratosis palmaris, as in the patient of Cummer (ADS 49 448, 1944) See Pachyonychia (p 1047)

The obese and the arthritic may not be able to reach their nails to attend to them, so that overgrowth, often caused by or complicated with onychomycosis, comes from neglect

Included within the broad connotation of onychauxis are the nail changes in acromegaly and the hippocratic nails of clubbed fingers. While clubbing of fingers is generally associated with pulmonic and circulatory troubles, such as emphysema, chronic bronchitis, tuberculosis rheumatic heart disease and decompensation it has been known to occur in ca of the lung, infective hepatitis, deformity of the thoracic cage arthritis, occlusive vascular disease and various other conditions, and it also may occur in the absence of obvious pathologic states, sometimes as a familial trait (Jackson: BMJ 1: 216, 1949) The etiology is obscure M er (AmHeartJ 34: 852, 194) concluded that for the development of clubbing low oxygen tensions must occur in tissues which are warm and in which the blood flow is greater than normal. A case of unilateral clubbed fingers was reported by Rodgers (BJM 2: 439 1941) who reviewed the literature on this rare condition.

ONYCHOGRYPOSIS is a term applied to extreme cases of hypertrophy in which the affected nails become greatly elongated and curved or clawlike. As a rule only 1 nail, usually that of the great toe, is involved, but sometimes several are affected. Various causes, including stasis, ichthyosiform eczema, tinea, psoriasis and trauma, may be operative; the disease is not an entity (Fischer AfDuS 193 661 1933) Interesting cases include those of Strandberg (ActaDV 1 : 471 1936) in which the condition was associated with exfoliative dermatitis; and of Durdon (BMJ 1: 723, 1939) aged and insane cardiac patient.

In treatment, if nail nipper and electric drill do not suffice to give relief, ablation of the nail may be undertaken. Reconstructive surgery with grafting of nails was described by Swanker (ADS 57 255, 1948) An aged arthritic patient with amazing onychogryposis was treated by avulsion of the nails by Porteous (BMJ 2 851 1954)

Pterygium is abnormal adhesion to the nail plate of the epidermis overlying the proximal nail fold. The disorder may be congenital, or acquired through neglect or from continued exposure to x rays, being a typical manifestation of roentgen dermatitis.

Adhesion of the cutaneous horny layer to the nail plate occurs in leprosy neuritis, sclerodactylia, and various atrophic conditions (Pardo-Castello) Edwards (NEngJM 239 362 1948) reviewed the changes found in arterial disease In arteriospastic disease he noted thinning of the nail fold and widening of the cuticle, with loss of the normally abrupt demarcations between the nail fold and cuticle and between the cuticle and nail plate such pterygium being characteristic of severe Raynaud's disease and constant in scleroderma

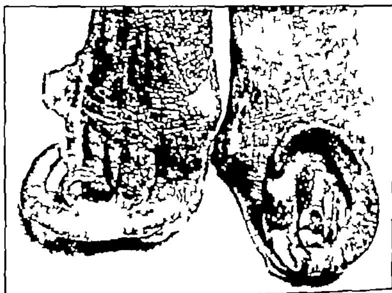


Fig. 1878 —Onychogryposis in a woman incapacitated by arthritis (Wien and Perlstein ADS 28 307 1933)



Fig. 1879 —Syphilitic onychia and paronychia in a woman 44 years old, who had no other cutaneous evidence of syphilis (Dr Grover W Wende)

In arteriosclerosis obliterans ischemia causes distortion and onychauxis, but nail fold and cuticle changes do not appear One may cut away the excess with suitable scissors and push it back with a blunt clean instrument.

Onychia, inflammation of the nail bed usually occurs as a result of trauma and pyogenic infection. Hollander (ADS 4 368 1921) reported * cases from which he isolated *B coli communis* Onychia may result from local infection the presence of foreign bodies or focal infection

Hemorrhage beneath the nail follows crushing injuries, the pain of which is markedly relieved by releasing pressure by cutting a window in the plate

It also occurs in purpura (q v) and may take the configuration of a longitudinal stripe red at first, turning brown, the splinter hemorrhage seen in trichiniasis (q v) Dermatitis medicamentosa was the cause of subungual purpura in the case of Oliver and Zakon (ADS 48 213 1943)



Fig. 1660—Lichen planus affecting the nails (Dr D. E. H. Cleveland.)



Fig. 1661—Psoriasis affecting the nails. (Dr D E. H. Cleveland.)









Fig. 1662.—Psoriasis of nails. (Dr F Ronchese.)
Figs. 1663 and 1664—Verruca of nail fold
Fig. 1665—Streptococcic paronychia, same bacterium in dermatitis and dental bacuss.

Local Inflammation of any kind capable of affecting the digits influences the nails of involved fingertips. Dermatitis venenata was the cause in the case of Cornbleet (ADS 36 231 1937) The accidental incidence on the distal phalanges of systemic dermatoses, such as psoriasis (White UCutRev 42: 592, 1938; Crawford ADS 38 583, 1938) and lichen planus (Vero ADS 26 677 1932 Gardner et al : AD 71: 636 1955) has its effects.

PSORIASIS is often associated with nail disease. When the nails alone are affected, the changes are the same as when the nail involvement is only a part of the patient's psoriasis. There occur detachment of the plate, alterations of the plate likely to end in partial destruction of the nail, *changes in color shortening of the nail and pitting*

The free end loosens first, and the plate is elevated from its bed. The plate thins and becomes yellowish brown. The free extremity of the nail seldom extends beyond the digital pulp, the nail being shortened and less energetic in growth. The yellow or brown coloration seldom affects the whole nail, but occurs either on the free edge of the detaching nail or at the side in a small, circular pit which is concave distally Friability may accompany the color change The nail may atrophy ulcerate along the free edge, and shrink to a mere to 4 mm. length. The edge of the shrunken nail is yellow and elevated from the bed, which itself is covered with a small amount of keratotic débris. Punctate erosions, which are alterations of less severity than those previously described, are usually numerous when they occur Their presence gives evidence that psoriasis is a disease of internal origin. When the digital skin is affected about the growth zone of the nail, transverse bands result, and, if the process is a lasting one the nail may be shed. Striae detachment, shortening or riddling with pits may be seen. In treatment, x ray is effective, and 3% tar with 5% ammoniated mercury and chrysarobin ointments and débridement are useful measures (avoid eyelids with fingers smeared with chrysarobin!) Treatment must also be directed energetically at other manifestations of psoriasis.

ONYCHOLYSIS SEMILUNARIS PURULENTA was described by Stühmer (Hautarzt 4 1E 1933) as a purulent form of onycholysis caused by pyogenic bacteria beneath the nail plate. A dull red spotty erythema becomes confluent under the otherwise normal appearing nail, without reaching its free margin. It remains well defined near the lunula, slowly progressing over a period of weeks or months. Pus may lift the nail plate from the bed, and episodes of acute inflammation may result in almost complete detachment, although the lateral and margins always remain fixed. In such cases I should perform appropriate débridement, and out and eliminate focal infection and make use of antibiotics given orally

Paronychia is characterized by acute or subacute inflammation of the periungual tissues of 1 or more of the nails. The process may be peripheral, but sometimes the disease undermines the nail even to the extent of causing it to be shed. Micrococci are the usual causes, and focal infection, especially of the teeth, is significant in recalcitrant cases. Trauma, foreign bodies, syphilis and dermatitis of the hands (q v) are other possibilities. Cases have been reported due to many agencies, including tuberculosis, blastomycosis sporotrichosis leishmaniasis and fungi. Rockwood (NEngJM 909 29, 1933) found many varieties of fungi in her cases (see Mycotic paronychia) All kinds of infections may be inoculated into finger tips warts as well as cocci having been introduced by dirty manicuring instruments.

When a purulent pocket lies adjacent to the lateral border of the nail beneath the nail fold provoking local swelling redness and pain, it is simply an impetiginoid lesion in the crevice pointing toward the nail. Soak the digit in hot water for a few minutes to soften the tissues, then put into the fold the point of a scalpel, the cutting edge away from the nail Move the point gently back and forth in the nail fold, pressing it deeper until it painlessly opens the purulent pocket. Hot soaks and an antibiotic ointment will complete the cure

Diffuse paronychia in contrast with the local abscess described above is not so easily cured. It is often streptococcic or mycotic in origin, rather than staphylococcic and it may depend on foci of infection as pustular dermatitis does. Elimination of foci x ray therapy *antibiotics* and correction of nutritional and endocrine deficiencies are useful therapeutic measures Three per cent chrysarobin in chloroform a practical and valuable medication I use often was introduced for the purpose by Morrow and Lee (J Cutl) 278 1015)

Destructive cases of great chronicity and severity are fortunately rare like that of Butterworth (ADS 68 474 1953)

See Gonorrheal keratoderma Gangrene, ascular Chiroe [illegible] festation; Schlesinger [illegible] [illegible] biChir 48 436 1921) treatment Stokes (ADS 7 44 1923), tuberculosis; Haden [illegible] blastomycosis; Harvey [illegible] (ADS 31, 1923) focal infection, Hicks (Lancet 1 67, 1941), leishmaniasis 81 218, 1939) tincture of iodine Costa (ADS 49 191, 1944)

Hangnails are torn filaments of epidermis, lying free distally and attached proximally so as to tear deeper as they are pulled back. They constitute commonplace inflamed and painful fissured lesions of the skin about the nail

folds (Hart AmJSurg 46 711 1939) Low humidity and the overuse of detergent and defatting agents are provocative Chewing and picking at the skin and nails promote their development. In treatment, one may flatten the filament and secure it with flexible collodion (Pardo-Castello) With a razor blade, one may notch the skin in a wedge shape proximal to the hangnail so as to remove the tag and to reform the lesion from a tearing one into a simple wound, which may be touched with an antiseptic

NEUROPSYCHIATRIC DISEASES AFFECTING THE NAILS

Onychophagia (Biting of the Nails) is a neurotic habit. It causes deformity of various degrees, and it apparently provokes the nail to speedier growth than normal (Clark and Buxton BJD 50 221 1938) Maceration, hangnails, paronychia and infection are commonly associated with this unfortunate habit. Keeping the nails carefully manicured so as to help the child gain a desire to keep them looking attractive is reasonable psychotherapy, the habit is a hard one to cure. It is often transformed into the habit of chewing the buccal mucous membrane, or smoking gum chewing trichotillomania or some comparable tic. Elevation of the occlusal surfaces of the posterior teeth by means of cement is an ingenious method advocated by Prinz and Greenbaum (Diseases of the Mouth, Lea & Febiger 1935, p 250) to make it impossible for the patient to bring his incisors together Students of child behavior would be more concerned with therapy applied to the parents, who should avoid rejection, overambition for the child and too much frustration of the whims of immaturity

Nail biting was followed by secondary Vincent s infection of the skin and gangrene in a 7 year-old girl seen by Hultgen (J 55 857 1910)

Onychotillomania, or neurotic picking at a nail until it is permanently altered has been recorded by Alkiewicz (DWchn 98 519 1934) This can be a manifestation, as I have observed in several patients of delusion of parasitism (q v) and such a case was described by Combes and Scott (ADS 63 778 1951)

Organic Nervous Disease can cause nail changes, as in tuberculoid leprosy or syringomyelia. See also Causalgia and Glossy skin. Atrophy of the nails consequent to war wounds was discussed by Le Dantec (JMédBordeaux 89 215 1918) Trophic changes were described by Zeisler (JCutD 19 511, 1901)

COLOR CHANGES IN THE NAILS

Pigmentation of the Nails.—The normal color is that of the skin (q v) and is largely made up of the color of the blood masked by the translucent nail plate abnormalities of which alter the color seen. With respect to the hue of hemoglobin, the nails are pale in anemia red in polycythemia, bluish red in cyanotic patients and abnormal in vasospastic conditions.

Dystrophic onychogrypotic and mycotic nails are variously discolored, being dark, blackish brownish greenish or gray

Yellow nails result from tobacco-staining most often; nitric acid will discolor them also, and picrates used in making explosives. One would think of carotinemia and jaundice as possible causes. Yellow coloration followed mercurial therapy for syphilis i man seen b Sibley (BJD 23; 248, 1911) ffecting only the nails not the skin, and event ally dis ppearing Resorcinol and Eucesol stained the nails orange when nitrocellulose-containing lacquer was used concurrently noted Loveman and Fliegelman (AD 72: 153, 1935)

Secondary infection of dermatitis of the fingers with *Ps. aeruginosa* caused deep green pigmentation of the nails in the case of Goldman and Fox (ADS 49; 136, 1944) The same bacterium and also Candida were found in the green nails studied by Moore and Marcus (ADS 64 499 1951) Strains of Aspergillus, Penicillium, Alternaria and Rhizopus are often found in cult res from discolored nails, t the greenish, brown and dirty discoloration of which they doubtless contribute

Black discoloration of the nail may be caused by *Ca dida albicans* strains that grow black in vitro. The edges of one o several nails may be affected, with involvement of the plates to various degrees. I have seen a few cases in which the entirety of many nails was involved.

Blue discoloration from Atabrine was commonly seen in patients with lichen planus, atypical, Southwest Pacific type (q v); see also Dermatitis medicamentosa, quinacrine.

Brown discoloration and retardation of *growth resulted* from intoxication by gold given in the treatment of arthritis, reported Simons (AfDuS 178: 400, 1930). Phenolphthalein is said to have led to nail discoloration (Pardo-Castello, 1936) Subungual hemorrhage discolors the nail.



Fig. 1886.—Black nails from subungual and ungual Candida infection
Fig. 1887.—Partial leukonychia. (Dr O. G. Costa.)



Fig 1888.—Leukonychia, involving all nails. (Dr Rene Gombner)



Fig 1889.—Leukonychia totalis see Fig 1890 (Stubenbord and Rubenbord ADS 11 761 1938.)



Fig. 1890.—Leukonychia totalis, toenails of patient abo n l Fig 1889

Mercury sulfide accounted fo blackness of the nail in the case of Callawa (AfD 38 6, 1937) Amm niated m re ry ointment used on derm titi of the fingers causes gun metal discoloration of nails. Permanganate of potassium, commonly used for soaks

stains the nails mahogany brown; in fact, the depth of coloration is the practical means of estimating whether the solution the patient uses is of proper strength. Staining is considerably *less when this useful medicine is prescribed in the form of poultices rathe* than soaks. The discoloration can readily be removed by making a paste of baking soda in water and rubbing it on the nail. Chrysarobin stains the nails yellow brown.

Violaceous transverse bands have been described as a sign of syphilis (Milian); this "lilac arc" is stationary on the nail bed and does not grow out, and such marks occur on 1 o several fingers asymmetrically affecting the middle and ring fingers preferentially.

Transverse bands of melanotic hyperpigmentation have followed x ray therapy used for dermatitis of the hands (Sutton: J 150: 210 195.)

Pigmented bands may also occur as longitudinal striations (q.v); roentgen dermatitis, arsenical keratosis and nevi may lead to their production. Unevenness of pigmentation in the Negro results commonly in longitudinal pigmentation in nails.

Loss of Translucency of the nails may be secondary to anemia, and also to chlorosis, angiospasm, polycythemia icterus and pigmentary diseases. Thickening of the nail plate or increase of the subungual horny layer may destroy the translucence and a growth of monilia or other fungi could produce the same result; see Pigmentation of the Nails.

Leukonychia (Leukopathia Unguium) signifies whiteness of the nail plate and is characterized by loss of transluceney of the nail because of incomplete keratinization of the horn cells. These contain droplets of a substance which has not been converted into keratohyalin, so that the affected area is white for the same optical reason that milk is white The condition may be partial or total and may be manifested in transverse or longitudinal bands or in a puncti form disposition. Discrete small, scattered lesions are called gift spots.

Whiteness is due not to air bubbles, as was once believed, but rather to imperfect cornification (Singer ADS 24 112 1931) Gift spots are not to be mistaken for the whitish patches of onychomycosis (Leukonychia trichophytica q v) Trauma, particularly by manicuring is a factor in their production in some instances (Frohn: DZtschr 74 136 1936) One or more nails may be affected. The lesions usually appear near the lunula and progress toward the free border with the growth of the nail.

Reporting an intensive study of gift spots occurri g in his own nails for a period of 1 year Mitchell (BJD 65 121, 1953) also reviewed the literature on leukonychia. Man of his punctate lesions grew out to the free edge of the nail and were cut off Some of them disappeared without reaching the free edge. Many made thei first appearance ove the lunula, but some first appeared more distally When they first started, they were ill defined, pale and semi translucent, becoming mo clearly demarcated, white and opaque they developed When a spot would fade, it might do so quickly within a few days. M t hell found it impossible to predict of a spot whether it would fade grow reach the edge or f il to do so. No spot appeared in his toenails during a period when o 100 appeared on the fingernails. Seeking these lesions in the nails of newborn infants, he found none and this would be understandable if they were caused by trauma. In infants 3 months old, he frequently found transverse bands representative of the metabolic disturban e attendant upon birth and the assumption of extrauterine life.

The association of leukonychia with upper respiratory infection was noted by Josephson and Lerner (ADS 29 703 1934) and with hepatic cirrhosis by Terry (Lancet 1 757 1954) A ground-glass appearance, rendering the lunulas indistinguishable was observed by Terry in 82 of 100 patients with cirrhosis of the liver

Transverse white stripes are simply a form of Beau s lines (q.v) They marked each attack of relapsing fever in a case observed by Montgomery (CalifM 68 29 1948)

Longitudinal white stripes are quite rare representing the analogue of vitiligo of a fraction, large or small, of the growth zone of one or more nails a case was noted by Marquez (AnndeD 10 658 1939)

Leukonychia Totalis is the curious disturbance manifested by whiteness f the whole nail plate f all nails. In many cases, such as those of Fox and Fiske (JCutD 35 539 1917) Eller and Anderson (MJ&Rec 127 318, 1928) Becker (ADS 21 957 1930) Stubenbord and Stubenbord (ADS 32 761 1935) nd Kruse et al. (JID 1 123, 1951) the deformity was hereditary usually a simple dominant (Cockayne Inherited Abnormalities Oxford U Press, 1933 p. 27") Acute total leukonychia has been observed in some 20 instances that have been recorded, 1 of which was the patient of Bernstein and Goldberger (ADS 57: 54. 1948); in this boy 16 years old, the nails turned white in a period of 3 weeks.

THE SEBACEOUS GLANDS

See also Anatomy Embryology Physiology Seborrhea Comedo Acne vulgaris Sebaceous cyst Milium Pilosebaceous adenomas Sebaceous carcinoma

ASTEATOSIS XEROSIS

Xerosis is a condition characterized by deficiency of sebum As a primary disturbance it is associated with ichthyosiform and hypohidrotic ectodermal defects Symptomatic hyposteatosis occurs in senility hypothyroidism, estrogen deficiency malnutrition avitaminosis, diabetes, scleroderma xeroderma pigmentosum, ichthyosis, leprosy glossy skin scars of burns, roentgen dermatitis, pressure atrophy and dermatitis due to fat solvents, alkalies, such as strong soaps and washing powders and other astringent or inspissating agents, such as alum and formaldehyde Localized asteatotic dermatitis venenata results in dryness thickening loss of flexibility pruritus and fissuring

Prognosis depends on the causative factor and on permanency and degree of damage or deficiency of the sebaceous apparatus. Lubricants, such as cold cream or a mixture of petrolatum and hydrous lanolin are indicated. Low humidity contact with wool and excessive use of soap are to be avoided. Compare xerostomia

FORDYCE'S DISEASE

The lesions are tiny symmetrically grouped, pinpoint to pinhead size yellowish or chamois tumors which generally lie flush with the surface of a mucous membrane. Patches of considerable size may be present. The inner surfaces and vermilion borders of the lips, especially of the upper lip, frequently are affected (Fordyce JCutD 14 413 1896) Within the mouth the site of predilection is about the opening of the parotid duct I have seen cases involving the shaft of the penis and the areolae of the nipples. Symptoms are usually lacking The tiny masses consist of anomalous, hypertrophic sebaceous glands (Sutton JBIRes 14 489 1914 Chambers ADS 18 666 1928) The condition is a common one according to the statistical studies of Halter (AfDuS 176 201 1937) It is harmless. Discovery of its presence is usually accidental. No treatment is necessary Patients are sometimes startled by their discovery of the condition, and require reassurance.

Heterotopic sebaceous glands formed a 2 mm. nodule of the tongue in a case seen by Guiducci and Hyman (ADS 70 349 1954)

See White (JCutD 23 97, 1905) Margolis and Weidman (ADS 3 723, 1921) Montgomery [illegible] and incidence, Goeckerman (ADS 14 60 1926) McCarthy (Histopathology of Diseases of the Skin, Mosby 1931, p. 363)

RHINOPHYMA

Rhinophyma is characterized by the development of firm, lobulated, thickened, purplish masses of rugose integument on the nose as a result of chronic and extreme hypertrophy of sebaceous glands. The tissue consists of enormous sebaceous glands their ducts patulous and engorged with seborrheic material. The course is slowly progressive. Severe cases affect men almost exclusively and alcoholism is a common but not an invariable causative factor Symptoms are generally absent, except the conspicuous deformity although acneiform or roseacea like pustulation may be bothersome.

The patient of Ginsburg (ADS 32 468 1935) was a woman, which is unusual and the female patient of Sams (ADS 26 834 1932) showed involvement of the chin as well as the nose A man with extreme involvement wherein the ears, too were affected and total alopecia was present, made a notable response to testosterone reported Ayres and Jensen (ADS 56 279 1947)

There is no doubt that such hypertrophy of fat glands represents endocrinopathy I have been treating my cases with x ray therapy in doses of ... and with estrogenic substances in large dosage with some benefit since it has





Fig 1891.—Fordyce's disease Section from buccal mucosa, showing sebaceous gland and duct.

Fig 1892.—Rhinophyma. (Dr J Lamar Callaway)





Fig 1893.—Rhinophyma.

Fig. 1894.—Rhinophyma. (Dr Grover W Wende.)

become generally known that fat glands are diminished in size and activity by these hormones (see Acne treatment) In extreme cases, the treatment is surgical. Excessive tissue is simply pared off with a razor until the nose is properly shaped epithelization is rapid under a pressure dressing (Grattan MRec 98 665 1920) Klauder (ADS 33 885 1936) used unipolar desiccation.

See White and Warren (StPaulMJ 5: 887 1903) treatment Wende and Bentz (JCutD 22 447 1904) startling case, 5 tumors on nose, Boroller (ba JCutD 33: 428, 1915), treatment by electrolysis, Clark (UCutRev 25 63, 1921) desiccation; Hanrahan (BullJHH 49 1931) surgical treatment; Novy (ADS 22: 270 1930) unique case with superimposed squamous carcinoma Eller (NYSJM 33 June 15, 1933) surgical treatment.





Fig 1895.—Rhinophyma. See Fig. 1896. (Dr James F Grattan.)
Fig. 1896.—Rhinophyma, after plastic surgery

ACNE VARIOLIFORMIS

Synonyms—Acne necrotica Acne frontalis Acne atrophica Papulonecrotic tuberculid (some cases) Dermonecrotic furuncle (some cases)

Symptoms.—Acne varioliformis is a chronic inflammatory disorder characterized by the development of papulopustular lesions, which frequently involve the follicles and are always followed by more or less varioliform scarring The disease is comparatively rare The sexes are about equally affected. The majority of the patients are adults. The lesions are discrete but usually grouped pinhead to pea-size papules or nodules, slightly elevated and pale reddish in color They develop slowly and ultimately undergo central necrosis and occasionally pustulation, with the formation of brownish, tightly adherent crusts. The majority of the papules are pierced by hairs, and concomitant seborrhea is frequent. Within a few days the crust becomes detached, and a small rounded atrophic scar is exposed. Many cases exhibit a tendency to grouping and linear or circinate patches may result. The scalp, forehead, nose and cheeks are favorite sites, although in rare instances the trunk, and even the extremities, may be involved Typical cases are almost asymptomatic The course of the disease is persistent, and the repetitious development of new lesions may continue for months or even years.

Etiology—Little is definitely known. Johnston (PhilaMJ 1899 p 128) considered it a tuberculid, and Sabouraud (AnndeD 10 845 1899) held that it is due to the conjoint action of his microbacillus and ordinary staphylococci. Schamberg (JCutD 20 99 1902) found Sabouraud's bacillus on apparently normal skin. The staphylococcus is probably actually the cause, but one is constrained to hypothesize a special strain or a peculiarity of the soil, for acne varioliformis is distinguishable from furunculosis. A case was cured by Engman and Mook (JCutD 31 269 1913) with staphylococcus vaccine. In a case with concomitant furunculosis, staphylococcus toxoid appeared to cure the acne varioliformis, but it did not influence the boils, reported Baer (ADS 38 122, 1938) One may surmise that immunity to exotoxin may be separate from ability to eliminate the microorganisms.

There are at least 2 kinds of acuminate centrally ulcerating acute inflammatory lesions of the skin, productive of scarring: (1) those due to necrotizing staphylococci, and (2) those due to tuberculous allergy They can be distinguished clinically by the tuberculin reaction, which is positive in high dilution i the on ; and by cultures, which should reveal virulent staphylococci productive f exotoxin in the other The lesions are follicular but they are not built about comedones as ordinary acne is. A case typical of the papulonecrotic tuberculid was presented by Bechet (ADS 36 807 1936); the tuberculin test in this patient was positive in a dilution of 1:1,000,000.





Fig. 1897—Acne varioliformis, showing typical lesions in a common location The pustules are not so closely grouped, as a rule (Dr Isaac R Pels)

Fig. 1898—Acne varioliformis, scars, in a case of 8 years' duration.

Pathology—The lesions re commonly but not invariabl f llicula (Pick AfDuS 1899 p. 651) and re charact rized by localized foci f dense round-cell infiltration in the upper dermis, usually surrou di g a follicle with subsequent necrosis, and sloughing o mass of the ove lying pidermis. Epithelioid cells nd tuberculoid structure are seen in many cases. The coil glands and ducts re in olved only by accident nd the inflamma tory process is more superficial than in hidradenitis suppurativa. Strumia (ADS 10 703, 1924) produced typical experimental lesions by the intradermal i jection of staphylococci and streptococci. The painful nodes in cases of Balog (AfDuS 176: 446, 1938) under went central necrosis after thei onset with chill nd fever; th lesions were thought metastatic, and Balog amed the condition Benign l farcti g pyemid.

Diagnosis.—The disease is to be distinguished from acne vulgaris and pustular syphilis. The localization and paucity of the lesions, and the peculiar character of the scarring should serve to prevent confusion with the former and the absence of other signs of syphilis should eliminate the latter (Sulzberger ADS 38 122, 1938)

Prognosis.—Untreated, the disease may persist indefinitely and even under treatment its recalcitrance is notable The disorder was of 4 years duration in the patient of Bechet (ADS 41 969, 1940) when it finally yielded to moist saline compresses, bacteriophage and injections of liver extract.

Treatment.—Internally measures aimed at improvement of the patient's resistance to infection are indicated. Staphylococcic vaccine has been found serviceable The condition of 1 of White's patients was greatly benefited by large doses of Fowler's solution. The woman suffering with acne vulgaris as well as varioliform lesions, reported by Felt (ADS 30 151 1934) received about 20 injections of autolyzed staphylococcus bacteriophage into the lesions and was later cured in 1 week with the use of ammoniated mercurial ointment.

Staphylococcus toxoid is particularly effectual (Wise and Sulzberger YBD 1937 p 386) Roentgen therapy generally succeeds (MacKee JCutD 30 911, 1912) One would, of course clean up focal infection. Local treatment with ammoniated mercurial ointment or with sulfurous preparations has been recommended (Crawford ADS 40 106 1939) Aureomycin ointment was found effective by Howell (ADS 62 705 1950) An antiseptic mixture of sulfur 2% and chloramphenicol 0 6% in Vioform Cream has cured several of my patients who were given x ray therapy too.

THE APOCRINE GLANDS

LICHENOID ERUPTION OF THE AXILLAE FOX FORDYCE DISEASE

Lichenoid eruption of the axillae is a rare chronic itchy disorder affecting women almost invariably and characterized by a persistent eruption of small discrete dry papules located symmetrically in the axillary regions, sometimes about areolae of the nipples pubic or sternal areas. The original description of 2 cases in women was given by Fox and Fordyce (JCutD 20 1 1902) Itching is the earliest symptom. It is almost intolerable and is extremely recalcitrant to therapeutic effort. The lesions develop slowly and do not regress spontaneously There is some hyperpigmentation of the involved regions, partly due to excoriation. The texture of the skin is little altered except by the presence of the firm papular lesions, which are not scaly They are located at the orifices of hair follicles.

Cases in males have been described, although they are rare That of Kaufman (NYSJM 38 1 1938) was the fourth on record, and 1 of Zakon and Goldberg (ADS 64 659 1951) was typical but not extreme

Etiology—The cause is unknown Histologically Fordyce (JCutD 27 157 1909) found papillary hypertrophy and edema, with perivascular lymphocytic infiltration. Epidermal changes consisted of some acanthosis and parakeratosis which obstructed the glandular orifices. Cystic dilation of the apocrine glands was also demonstrated by Fischer (DWchn 60: 821 1925) according to Way and Memmesheimer (ADS 39: 377 1939)

One may think of analogy with the sweat retention syndrome the abnormality in Fox Fordyce disease being concerned with apocrine rather than with sweat glands, obstruction and distention being productive of severe pruritus because of differences in innervation. Spiller and Ritchie (ADS 44 1061 1941) noted resemblance of histologic changes to those of chronic cystic mastitis a disease in which androgenic medication is helpful.

Apocrine anhidrosis was found in patients investigated by Shelley (AD 71 1 1955) for they lacked the axillary odor and the local injection of epinephrine did not excite sweating from the apocrine pores.

Treatment.—The view was long held on the Continent that the disease represents neurodermatitis (Alexander HandbHuG 6 1 433, 1927 Springer) but I see no justified doubt that it is an apocrine glandular disease in some way associated with endocrinopathy The patients, while apparently in normal health regularly are much better during pregnancy yet estrogenic hormones may intensify itching while androgen sometimes helps them considerably (Cornbleet ADS 65 12 549 1952) Stilbestrol seemed beneficial to Loxburgh (BJD 55 121, 1943) Roentgen therapy is a mode of attack of only poor effectiveness even if pushed until it produces atrophy Topical applications accomplish almost nothing In cases not helped by x ray one may inject the subcutis with 95% alcohol or with local anesthetics such as may be used in treating pruritus ani (QMIN J 109 2101 1937) Plastic surgery is worth while applicable and justified in some cases.

See Walt (DWch 74 592, 1922), cases; Whitfield (BJD 35: 391, 1923); Kreibich and Dreist (ADS 1 4 6, 19 4) Kleeg (DWchn 77: 1, 1924) Fox (ADS 10 1 19 1) ... Lowenberg (1 Wchn 11 1926 ... 1927) ... (AfDuS 151 16 1926) Hirschfeld (DWchn 82 231 1926) Chormak and Ostrowski (ActaD ... 1926) Len (DWchn 83 1627, 1926) Chormak ... 1927) in males ... Hoppe (DZtsch 1 105, 1927) Turk (DWchn 84: 326, 1927) ... Tiesklenecek 3 1 6 1927) Jung (DZtsch 51: 112, 1927) ... 1927) 71 ... pathogenesis Konrad (DZtschr 53 ... 1927) Hild (DWchn 107: 1112 ... 658, 1935) pathology Halter (AfDuS 176 201 1937) ... Spreiner (AfDuS 176 ... 1938) benefit ... (DWchn 1 146 1938) ... hormonotherapy ... cases in women with menstrual abnormalities; ... (DZtschr 77: 1 6, 1938)

x-ray and estrogen; Vero (ADS 53: 252, 1946) extensive involvement in a Negress. Cornbleet (ADS 54: 325, 1946) estrogen intensified itching. Arnold (ADS 54: 362, 1946) palliation with Fowler's solution.





Figs. 1899 and 1900.—Fox-Fordyce disease in a young Negress, showing axillary, sternal, and areolar distribution; pubis was also affected. Plastic surgery eventually relieved the patient.





Fig. 1901.—Fox-Fordyce disease, axilla.
Fig. 1902.—Fox-Fordyce disease in a man. (Kaufman: NYSJM 38: 1, 1938.)

HIDRADENITIS SUPPURATIVA

Synonyms.—Hidrosadenitis axillaris. Abcès tubéreux de l'aisselle (Velpeau). Hidrosadénite phlegmoneuse (Verneuil).

Hidradenitis Suppurativa is characterized by deeply seated acneiform or furuncular inflammation of the apocrine glands, particularly of the axilla but occasionally elsewhere. The review by Lane (ADS 28: 609, 1933) is especially informative.

Two diseases, in my opinion, manifest abscesses of the apocrine sweat glands. Apocrine acne is not primarily parasitic, and bears marked resemblance to acne conglobata (q.v.), some cases of acne cheloidalis and perifol

liculitis abscedens et suffodiens. The disease is, of course readily complicated with pyogenic bacterial infection. Apocrine furunculosis is a primary bacterial adenitis.

Apocrine Acne is a disease essentially of adults. It affects robust persons who are well nourished and developed, and it occurs without associated systemic disturbance or impairment of the general health, according to Brunsting (ADS 39 108 1939) excepting I note the lassitude of the hypothyroid individual, the tendency to obesity and the concurrent acne in 4 of Brunsting's 22 cases. Early lesions are a few small firm reddish, tender nodules. These increase in number and size and often coalesce to form typical cordlike bands. The pain they produce is variable and it may be so considerable as to limit mobility of the shoulder joint. Some nodules resorb, wholly or only partially leaving comedones, sebaceous cysts, pitted scars and bridge scars. Some suppurate indolently with foreign body reaction. Perianal pyoderma is hidradenitis (Marks SouthMJ 39 477 1946) Suppuration may persist and extend into the deep layers of the subcutaneous tissue with the formation of extensive sinus tracts, Brunsting (1939) continued Frequent remissions and relapses may occur and healing may be delayed for several months. The base of the ulcer is usually covered with little seropurulent discharge for suppuration extends beneath the surface Gangrene does not occur Fever and associated systemic reaction in connection with recurrent bouts of regional erysipelas are common. About the anus, extension of the disease process through the deep tissue may continue so as eventually to perforate the rectum and to form anal fistulas, as described by Geber (in Ziemssen's Handbook of Diseases of the Skin, Wood, 1885 p 490)

Apocrine Furunculosis.—This type of hidradenitis, which may be primary or more often secondary to apocrine acne is the manifestation of acute or chronic, relapsing painful pyogenic infection. Cherry size, pus-containing lumps form and their thick, greenish yellow purulent content may find egress at the surface or it may burrow and form interconnecting subdermal sinuses. Primary hidradenitis is often incited by staphylococci abetted by the application of an ointment to the axilla.

Etiology.—Women are more commonly affected in my experience but they were a bare majority 12 of 22, in Brunsting's series. The age of his patients ranged from 16 to 48 I have thought that shaving the axillary hair plays a part I am sure that the application of unguents to this region does sometimes lead to glandular infection, furunculosis and abscesses; but apocrine acne and furunculosis are distinct diseases. I saw staphylococci among the leukocytes of previously unopened abscesses in patients with acneiform lesions Brunsting reported the presence of microaerophilic hemolytic streptococcus in 6 cases, and in others *Staphylococcus aureus* and *Streptococcus viridans*, which occurred more commonly See Acne vulgaris Furunculosis.

Pathology.—One obtains tissue for microscopic examination ordinarily only from patients whose severe disturbance justifies surgical incision or wide excision of abscessed and deformed tissue In this, one sees acute purulent inflammation with cystic distention of the deep part of the glands, destruction of the epithelial lining and micrococci in the pus. In 5 cases of sweat gland abscess, Koch (ArDuS 176 307 1938) described the early changes, finding bacteria in the lumina of the glands, and reactive purulent inflammation. He thought that apocrine glands are more susceptible to infection than other glands because of the alkalinity of their secretion I do not know of a description of the microscopic structure of the comedones and sebaceous cystlike lesions of the quiescent stage of the chronic apocrine acne

Treatment.—Each patient presents an individual therapeutic problem, as Brunsting has said In the chronic state when recurrences of acneiform lesions are annoying but not disabling the best treatment is as for infected acne with diet thyroid estrogenic hormones, antibiotics and roentgen therapy

Cysts may be excised, or simply let alone No ointment should be applied to the region. A lotion, such as 1% phenol with 1-5 000 bichloride of mercury in 70% alcohol, is useful for topical application.

When the disease has caused gross deformity plastic surgery is required. When pyogenic infection is active treatment must meet the surgical indications. Excision may be advisable. Rest, incision and drainage, Dakin s solution, radiant or moist heat, roentgen therapy staphylococcus toxoid, sulfonamides, penicillin and sedative medication may be used as recommended by Tachau (ADS 40 595 1939) Presently tetracycline is my preference.

See Politzer (JCutGUDis 10 9 1892) "hydradenitis destruens suppurativa, nodular lesions of face and neck agreeing with description of Verneuil (ArchGén 2 537 1864); Cole and Driver (ADS 19 310 1046, 1929) case; Sutton and Sutton (Diseases of the Skin, Mosby Ed 9, 1935, p 1166); Brunsting (PSMMC 12 763, 1937); Wien (ADS 42 1142, 1940) case involving man axilla and groin Grund (ADS 43 178, 1941) keloidal complication in Negroes with axillary pubic and perianal lesions Hagelfried and Nolan (WestVaMJ 38 393, 1942), case Fried (abs J 118 920 1942) x ray therapy Cooper (SouthMJ 41, 750, 1948), perianal; Brunsting (ADS 58 498, 1948) "I regard hidradenitis as an expression of acne in an exaggerated form" Wile and Curtis (ADS 58 746, 1948 62 329 1950) woman with Cushing syndrome whose acne, treated with plastic surgery later subsided after x-ray therapy of pituitary gland; Jackman and McQuarrie (AmJSurg 77 371, 1949) review of 288 M yo patients, emphasi on perianal aspects; Morgan (AnnWestMed 3 314, 1949) 2 cases; Proppe (ZbeihrHuG 6; 287 1949) Conway et al (SGO 95: 455, 1952) radical surgical therapy Goldsmith (BJD 62: 327, 1950), apocrin cne case; Schenck (Radiol 54 74, 1950), 58 cases, x ray thrice weekly to total of 1200 curative; Brunsting (ADS 65 303, 1952) relation to acne conglobata and dissecting cellulitis confirmed; Sutton (ADS 65; 311, 1952); Cornbleet (ADS 65 12, 1952) 3 cases improved during pregnancy; Wirth (Milbury 116: 208, 1952) axillary furunculosis and underarm cosmetics; Stalner and Grayson (AD 71 205, 1955), 23 acute cases, 22 chronic, half of the latter with cne relationship; Inman (BJD 67 20 1955) 33 year-old female, with acn conglobata also, impro ed markedly after hysterectomy and administration of estrogenic substance

THE SUDORAL GLANDS

See also Anatomy sweat glands Physiology sweating and sweat chemistry Sweat gland tumors; Sudoral carcinoma.

Determination of the Existence and Distribution of Sweating —Numerous tests have been devised for the investigation of sweating

The test of Minor (BerlGesPhysiol 43: 639 1929) depends on the reaction of iodi e with starch to indicate the presence of wate : paint the test area, after thoroughly cleaning and drying it, with a mixture of iodine 1.5 castor oil 10.0, and bsolute alcohol 100.0 Onto the skin, which now looks greasy dark, and yellow dust fine rice powder pressing it into pores with a soft cotton powder puff and fanning way the excess. The white and ivory-appearing skin manifests fine, blue-black dots at poi ts where sweat appears; such dots soon coalesce. Dripping spoils and t minates the test. The material is easy to wash off with soap. Using Minor's test, List and Peet (ArchNeurol 39 1228; 40: 27 1938) investigated these types of sweating:

THERMOREGULATORY—elicited by external heat, hot drinks, aspirin;
EMOTIONAL—elicited by emotional strain, or pain;
MEDICINAL—elicited by pilocarpine (12 to 16 mg by mouth) or Mecholyl (12 to 25 mg by mouth) [*have ½ gr atropine hypodermic ready as antidote*];
GUSTATORY—elicited by spicy foods;
SPINAL REFLEX—in transverse and other lesions of the cord.

They found variations in intensity and course and time of onset of sweating in normal persons, but symmetry is normal. Sweating is greater in fold and grooves, the axillary antecubital inguinal, and submammary regions; and it is less over prominent part such as the tip of the nose, elbows knees, and extenso surfaces. Points can be found at all levels in the central ervous system, from the cerebral cortex to the peripheral nerve endings, t which irritation may cause sweating

The test of Roth (PSMMC 10: 383 1935) used a saturated alcoholic sol tion of cobaltous chloride, which becomes pink when wet. That of Guttmann (KlinWehr 1937 p. 121) used powder of chinizarin mixed with sodium bisulfate sodium carbonate and rice powder and this turns bluish mauve when water is dded.

Mecholyl given intradermally serves as a test of integrity of postganglionic nerve fibers and so is usef l in identifying leprosy th anhidrotic lesions of which do n t respond to the drug (Arnold: InternatJLepr 16: 335 1948)

HYPERHIDROSIS

Hyperhidrosis is the excessive production of sweat. It may be idiopathic or symptomatic, recent in onset or of long duration, generalized or circumscribed, and unilaterally or otherwise systematically distributed. It is a com

mon symptom in disorders such as tuberculosis, malaria, brucellosis, Graves disease and diabetes. It is provoked by warmth, nausea, pilocarpine and vasodilators, such as alcohol and aspirin. Anxiety neuroses and nervous tension cause sweating usually of the volar surfaces and axillae rather than of the glabrous skin. Sweating is generally greatest in the regions normally rich in coil glands.

Volar and Axillary Hyperhidrosis.—The palms and soles of some persons are continually cool and wet they sometimes actually drip. This condition is regularly present in anxiety states and psychoneuroses with tension. Stutterers are likely to suffer from hyperhidrosis (Greene J 109 187 1937) I saw great numbers of cases among neuropsychiatric military casualties, and tried with diligence to relieve them, but was unsuccessful. Wet hands and feet are vulnerable to pompholyx and recurrent stubborn, eczematoid dermatitis of a sort which may be attributed to nerves if any dermatosis justly may be. See Psychosomatic aspects of dermatology

Surgical attack upon the sympathetic nervous system for relief of hyperhidrosis and acrocyanosis (q v) has been discussed by Roberts (BJD 46 126, 1934) Telford (BJD 50 641 1938) White (NEngJM 220 181 1939) Palmer (ArchNeurol 58 582, 1947), and others. The procedure is entirely justified in the extreme cases, provided that initial test-blocking of the nervous pathway shows that its interruption accomplishes the aim. Such cases were reviewed by Haxton (BMJ 1 636 1948) 12 of his patients having been treated by sympathetic section which afforded prolonged, possibly permanent, cures. Usually no cause can be found, he stated, but among known possible causes are irritative lesions of the sympathetic pathways. Chemical sympathectomy by injections of 95% alcohol was accomplished by Levine and Harris (AD 71 226 1955)

X ray therapy sufficient to stop sweating requires a dose that damages the skin and is analogous to x ray treatment of hirsuties (q v) Doses of 250 r monthly for 6 treatments were recommended by Pirie (CanadMAJ 34 301, 1936) 400 r was given twice and 300 r thereafter in doses spaced at intervals of from 4 to 8 weeks by Miescher and Böhm (SchweizMWchn 78 14, 1948) with good results from a total of 1 600 r in most patients with the complaint of continuous sweating but not in patients with intermittent sweating No harmful effects from such dosage were observed by Borak et al. (ADS 59 644 1949)

An ergot preparation was used to relieve successfully the congenital volar hyperhidrosis of the patient of Carson and Montgomery (JPediat 43 472, 1953) Ergot is a dangerous drug see Dermatitis medicamentosa. Benadryl or barbiturates may diminish the sweating of anxiety considerably Atropine is not useful Banthine an anticholinergic drug especially useful in the management of peptic ulcer was found to have valuable antiperspirant effects by Grimson et al (J 143 1331 1950) Control of sweating with this drug proved a valuable adjunct in treating dermatitis of the hands, reported Brown and Sandler (ADS 64 431 1951) Prantal, a related drug of similar action, is similarly useful (Nelson et al JID 17 207 1951 18 373 1952) Hexamethonium can be used for the purpose (Sommerville and Macmillan BJD 64 442 1952) but it is a potent chemical capable of causing abrupt hypotension and vomiting

Undiluted formaldehyde solution swabbed on daily may effectively control plantar hyperhidrosis (Shelley et al ADS 69 713, 1954 Peterkin AD 70 366 1954)

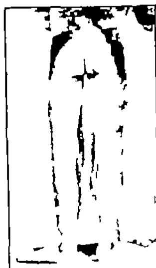
Underarm Perspiration.—Local applications are usually the best means for managing underarm perspiration (QMN J 141 168 1949)

"Topical applications attempt to accomplish one of two results—to overcome or [illegible] the object onable odor or to reduce the amount of sweat. [illegible] are usually [illegible] the latter purpose. They incl d such materials as tannic acid and the tannates [illegible] formaldehyd zinc salicylate aluminum chloride and aluminum phenol-sulfonat [illegible] be irritating and formaldehyde is a common sensitizer to the skin. Aluminum salts [illegible] destructive to clothes, but buffering them with urea helps t overcome this fault. [illegible]



Fig 1903.—Anhidrosis of left side of face, following resection of left superior cervical ganglion. (List and Peet Arch Neurol. 40: 27, 1938)





Figs 1904 and 1905.—Anhidrosis due to resection of sympathetic nerves. (Drs. List and Peet.) Fig 1904 Lesion of right internal carotid plexus causing sympathetic denervation of right supraorbital region, and anhidrosis. Fig 1905, Bilateral resection of second, third, and fourth lumbar ganglia, causing anhidrosis of buttocks and legs; note perilesionary hyperhidrosis in first lumbar distribution



Fig. 1906.—Hyperhidrosis of right sole resulting from faradic stimulation of right lumbar sympathetic chain distal to fourth lumbar ganglion, demonstrating the stimulation of sweating by this means (Drs List and Peet.)

deodorizing agents include hexamethylenetetramine, sodium perborate, zinc peroxide, oxyquinoline sulfate and others. They may be used in solutions, creams and powder mixtures. Essential oils and perfumes are used as masking materials. Hexamethylenetetramine may irritate and sensitize. Lamb has found sodium bicarbonate powder mixtures deodorant.

The common commercial antiperspirational and deodorant toilet preparations are in general harmless. If one brand proves to be a source of dermatitis venenata, another may not.

The mechanism of action of topical antiperspirants was investigated by Sulzberger et al. (ADS 60 404, 1949) who found no indication that the sweat ducts were narrowed by them. Aluminum sulfate preparations were apparently followed by the appearance of considerable cellular infiltration through the perpendicular portion of the eccrine ducts, perivascular cuffing of the upper dermis, some degeneration of the lining of the apocrine tubules, and desquamation of the epithelium thereof with the formation of cellular casts.

Localized and Unilateral Hyperhidrosis is an interesting phenomenon. The areas involved differ greatly in size and distribution. A lateral half of the face or even of the entire body may be affected as in cases reported by



Fig. 1907.—Circumscribed hyperhidrosis. The moist area is demarcated by the adherence of pencil-lead dust.





Fig. 1908.—Circumscribed hyperhidrosis.
Fig. 1909.—U hidrosis. (Dr. H. H. Hazen.)

Teuschler (ZntrlblNeurol 16 1028 1897) and others or the upper or lower half of the trunk, as in instances recorded by Kaposi (AfDuS 49 121 1899) and Mackenzie (TransClinSocLond 18 174 1884). The hyperactivity is confined to the glands located in certain nerve areas.

Sutton (J 59 1193 1912) had under his care a boy in whom the disorder was limited to an area about 5 cm. in diameter near the inner extremity of the left eyebrow. He also (JCutD 35 154 1917) observed an instance in which a palm-size area in the left scapular region was affected. The patient was a neurasthenic Italian who in moments of excitement, even during cold weather, would sweat in such quantity that a teaspoonful could be collected within 5 minutes.

Unilateral sweating results from neural lesions which stimulate sympathetic fibers, seen in epidemic encephalitis, lesions and tumors of the brain

stem, and unilateral frontal lobe lesions and sometimes in migraine (QJM J 106 487 1936) Aneurysms, new growths tabetic crises (band of sweating) and syringomyelia are listed as causative of localized sweating

Disturbances of local sweating due to various lesions of the central nervous system were reported by List and Peet (ArchNeurol 42: 1098, 1939); below the pons the fibers were ipsolateral. While cerebral lesions more commonly result in hyperhidrosis, spinal cord and peripheral nervous lesions more often produce anhidrosis, according to Piatus and Cuneo (abs BMJ 1: 136, 1939) Unilateral sweating of the forehead was relieved by section of the supraorbital nerve in the patient of Tarlov and Herz (J 133: 476 1947) A man with ninth dorsal disease of the spine sweated profusely over the upper half of the body and suffered flaccid paralysis of the lower extremities (Cornbleet et al.: ADS 60: 893 1949)

Gustatory Reflexes provoke curious patches of hyperhidrosis in some persons, such as a girl 22 years old whose right submental area was the site (Uprus et al.: Brain 57: 443, 1934) The reflex arc in this case was successfully broken by blocking the lingual nerve where it ran with the chorda tympani. Wende and Busch (J 53: 207 1909) Paroussaglan (JCutD 31: 515 1913) and others have reported instances of localized sweating which were evidently induced reflexly through stimulation of the olfactory and gustatory nerves. In the patient of Hall (IrishJMS 1953 p. 291) acidic foods that stimulated salivation also stimulated unilateral hyperhidrosis.

Asymmetric gustatory sweating of the face was first described by Baillarger in 1853 according to Langenskiöld (ActaChirScand 93: 294 1946) who analyzed 90 cases of this syndrome that had been reported in the literature and added 2 cases of his own. All these patients had suffered some sort of injury to a localized area of the head face or neck, commonly a necrotizing infection of the parotid gland, or had some disease, like syringomyelia, thought to have damaged the nerve supply to a portion of the skin. Eating or drinking was the accompanied with excessive perspiration in the area in which the nerve supply had been impaired. His explanation lay in the theory that the preganglionic sympathetic fibers governing sweating had been destroyed; thus, according to Cannon's law the postganglionic cholinergic fibers were rendered hyperexcitable and during mastication acetylcholine elaborated in the parotid gland diffused into the nerve endings in the skin and produced sweating (Mellinkoff and Mellinkoff: J 142: 901, 1955) Langenskiöld was unable to find report of any patient in whom gustatory asymmetric hyperhidrosis occurred below the neck.

The Auriculo-Temporal Syndrome is a rare sequel of parotid suppuration or injury first described by Frey (RevNeurol 2: 97, 1923) There develops after some weeks or months hyperemia with hyperhidrosis in the distribution of the auriculo-temporal nerve, attacks often developing in response to gustat ry stimuli, the disorder proving persistent and recalcitrant. This syndrome followed head injury with damage to the hypothalamus in a boy reported by Byrne (BMJ 1: 850, 1951); even the thought of food would provoke attacks.

Intermittent Hyperhidrosis, a rare disease, produces exhausting drenching sweats. Disabling attacks preceded by hypothermia occurred in the man described by Hoffman and Pobirs (J 120 445 1942) In the patient of Hines and Bannick (PSMMC 9 705 1934) it was necessary to replace chlorides to relieve exhaustion and to give atropine and Amytal to reduce central irritability

In the diabetic woman of Hull and Cameron (J 105 585 1935) drenching sweats occurred every 2 hours, day and night for 10 years, lasting for 10 minutes and coinciding with high blood sugar levels control was obtained with the administration of Sodium Amytal from 12 to 15 grains daily Excessive sweating in this essential hyperhidrosis is limited to circumscribed, symmetrically located areas, including the extremities, and is aggravated by warmth, excitement and emotional strain (Adson et al.: ArchSurg 31 794 1935) In 5 extreme cases, Adson et al. (J 106 360 1936) were constrained to perform sympathetic ganglionectomy which relieved the condition. The skin at once became dry and pink, but the glands did not undergo atrophy

Fibrocystic Disease of the Pancreas.—Infants with this disorder manifest abnormal sweating such that heat prostration is a significant hazard because of marked increase in electrolyte loss via sweat during hot weather (Conn ArchIntM 83 416 1949 Kessler and Andersen: Pediat 8 648 1951; Darling et al. AmJMedSci 225 67 1953 Edit J 155 128 1954)

Sweating Sickness is of historical interest. It occurred in explosive epidemics, strange unexplained and serious in the Middle Ages, with erythema

and glistening white lesions of miliaria, the rash being sharply demarcated at the wrist and not extending onto the hands (Tidy BMJ 2 63 1941; Zinsser Rats, Lice and History Little, Brown & Co., 1935)

GRANULOSIS RUBRA NASI

This is a chronic disease of the alar regions characterized by congestion, hyperhidrosis and well-defined, reddish, pinpoint to pinhead-sized macules and papules. Cases occur generally in delicate children. Hyperhidrosis is the constant feature, and may include the upper lip cheeks, forehead, and even the entire face and also the palms and soles. *The redness is diffuse poorly defined*, bright or dull in intensity disappearing on diascopy Telangiectasia is occasionally present. The papules are round, close-set, soft and distinct, never confluent. Pores are not present at their apices. Sometimes they are umbilicated, and minute pustulation may exist. Scales and cicatrices are absent.



Fig. 1910 —Granulosis rubra nasi. (Dr J E Lane)

Association with cold, cyanotic hands and feet is common. Abortive cases without papules are sometimes seen. Symptoms are practically wanting. There is no tendency to ulcerate The cause is unknown. There is some evidence that granulosis rubra nasi can be inherited. The disorder is a chronic and persistent one but tends to disappear on the approach of puberty I suspect that the ingestion of milk is concerned, for my patients seem to clear when this food is largely omitted. It is a plausible hypothesis that milk contains a hormone effective when ingested which importantly influences the *glands of the face (compare Acne)* Internally cod-liver oil and iron have been recommended. Locally astringents may be tried and x-rays prove curative in many instances (Beeson ADS 14 2.6 1926)

See Jadassohn (AfDuS 58 145, 1901) original description Macleod (BJD 15 181 1903; 18; 342, 1906), cases and review Lebet (A nde D 1903, p. 2 3) Fisher (DB 7 11 612, 1904) Ormsby (JCutD 23 183 1905) case; Mirolubow (I be Granulosis Rubra ... Inaugural dissertation, Bern, 1906), 68 cases on record (date, 33 of them Jadassohn ...) Gordon (JMK ... (DWchn 72 386, 1921) etiology Frost (ADS 6 219 1922) 4 cases

112, 1921), case Cockayne (Inherited Abnormalities, Oxford U Press, 1933, p. 379), heredity; Pavia (Hivelinfediat 33 394, 1924), case; Meschkilierson and Keradow (DMSchr 71 79 1926) over 120 cases recorded to 1933, authors saw 33 in 4 years; Tolmach (ADS 33 164 1936) 17 year-old boy Heller (BMJ 2: 1048, 1937) mother and daughter

BROMHIDROSIS

The offensive odor ascribable to sweating goes by this title, which comprises a part of the subject matter concerned with body odor the B O of twentieth century cosmetic advertising which has become part of the language. Sweat itself, freshly secreted, lacks odor entirely and is sterile, according to Shelley et al. (ADS 68 430 1953) who judged that odors laid to sweat are in fact due to fermentation. They believed that deodorant cosmetics succeed not because they check perspiration but because they are antiseptic. Their conclusions did not explain to my satisfaction why an individual may have little or no odor until immediately after he begins to perspire Lobitz suggested that such odorosity may come from bacterially contaminated apocrine sweat lodged in the follicular space until the sweat stimulus occurred.

Bromhidrosis may be general or local and, if eccrine is associated with hyperhidrosis. The axillae, genitocrural regions and feet are the regions commonly involved. The secretion may be excessive although not necessarily so. *Odorosity of sweat is thought to be a feature largely of the apocrine sweat.* These glands do not evolve until pubescence and degenerate in old age the axillary odor of the adult is not present in the child or in the senile individual. Persons differ with regard to the general development and activity of apocrine apparatus. Their odors are of variable strength, as well as variable in one person at different times.

There are undeniable differences between the smells of different races and peoples. To the Chinese the milk-drinking American is likely to smell like rancid butter The usual odor of the Negro differs from that of the white individual. An old maid does not smell like a young woman. The barnyard accompanies many a farmer into a physician's office.

A person's odor certainly depends on many factors, including his dietary habits, toilet customs, environment and clothing and the presence or absence of odorous disease involving the teeth, gums, nasal sinuses, physiologic and pathologic discharges and flatus. The tabetic whose bladder leaks smells of urine.

The odors of various diseases are said to be recognizable, such as those of pemphigus, uremia, measles and carcinoma. Decomposing epithelium has a typical odor Tinea versicolor imparts a recognizable musty smell. Acne patients smell alike. Symmetric lividity of the soles (q v) is highly offensive. Estrus in animals and menstruation in human beings induce odorific alteration. The body odor may be pleasant and agreeable, like violet or pineapple, as in cases described by Hammond (MRec 12: 460 1877) but as a rule it is *penetrating, sickening and persistent* and resembles that of putrid cheese. *The skin may* exhibit slight redness or tenderness or other manifestations of inflammatory and fermentative activity The combination of staphylococcus, hay bacillus and soggy interdigital epithelium gives rise to a characteristic, stinking caseous odor of the feet.

"Odors may originate from (1) gas escaping from the bowel without the knowledge of the person, (2) the breath, (3) discharge from the ears, (4) vaginal discharge, (5) decomposing sweat, sebum or urine on the skin or clothing, o (6) the peculiar odor of freshly secreted sweat. Certain foods and drugs are credited with producing sweat of a peculiar odor: alcohol, coffee, various ethers, garlic valerian asafetida and other gum resins, gelica, truffles, musk turpentine, tar sulfur, benzoic acid, iodine, iodides, phosphorus, zinc phosphate and copaiba are listed as having this power Nervous influence is also credited with the production or alteration of the body odor There are many reports dealing with neurotic or hysterical individuals who emanate peculiar odors, pleasant or the opposite, during attacks. Fraud must always be suspected. [Patients] should be examined for possible parosmia due to organic or functional nervous disease (QMN: J 112: 1406, 1939) See also Fetor oris.

Control of body odor may usually be *accomplished* by simple hygiene Chemicals for topical application to control sweating include methenamine 0.5% in a tragacanth lotion (Park *ADS 48 538, 1943*) salicylic acid, 2% in a powder vehicle, perhaps adding sodium hexametaphosphate 5% (BMJ 2 203 1940) and such astringents as aluminum phenol sulfonate, aluminum chloride and zinc phenol sulfonate in a cold cream vehicle (Weiss and Marcus

ADS 43 539 1941) Baking soda powdered under the arms does not stop sweating but deodorizes (Lamb JID 7 131 1946) See also Eller (MRec 154 167 1941) and QMN (J 112 1408, 1939 114 681 2238 1940 138 94 1948) One may use x ray therapy as in hyperhidrosis (q v) to treat bromhidrosis. In desperation, plastic surgery was recommended by Kahn (NYSJM 45 1555 1945)

In shaving the axillae which is helpful, one should use a dry razor on a dry skin and shave "with the grain. The astringents should not be used too liberally or frequently for part of the trouble they cause is to promote friction, so that dermatitis following their use may be mechanical rather than chemical in origin.

Parosmia.—Subjective experience of odor which may be offensive, and hyperosmia occur in disturbances of the olfactory tract and tumors of the hippocampal gyrus or uncinate process, and also in menopausal psychoses (Lederer: J 114: 631, 1940) Parosmia is often experienced during the aura of migraine. Bromhidrosiphobia (q.v) may be a manifestation of anxiety or of schizophrenia, and its prognosis is therefore widely divergent in various sufferers.

Symmetric Lividity of the Soles is characterized by macerated, wet, whitish or bluish red, slightly elevated, sharply defined, often bilaterally symmetric plaques on the soles usually involving the heels and about one-third of the adjacent plantar surface, as originally described by Pernet (BJD 37 123, 1924) Hyperhidrosis is present and the skin appears edematous and sodden, but vesiculation is absent. Symmetry is not invariable. The patient complains of tenderness. Adjacent to the lesions the shoes are more or less disintegrated by the sweat (Carney ADS 69 709 1954)

While local hyperhidrosis is an important factor the strong fetid odor typical of these cases, which are not rare, indicates that a fermenting agent is also concerned. Hitch and Hansen (ADS 38 881, 1938) however could not find fungi in scrapings or cultures from 4 cases. Their histologic study showed parakeratosis and hypergranulosis, edema, vascular dilation and moderate inflammation, mainly perivascular Symmetry of location made them think of neurologic relationships Kalz and Friedman (CanadMAJ 51 252, 1944) found the excessive sweat highly acidic. Cultures I have made have revealed only staphylococci, and I suspect the odor may be due to a digestive enzyme secreted with the sweat.

Treatment which is effective includes x ray therapy, the wearing of loosely fitting lightweight footgear and a salicylic acid and sulfur salve such as would be suitable for tinea and which palliates the evil odor satisfactorily Nelson (ADS 47 822 1943) recommended an astringent powder and KMnO soaks. Hopkins et al. (ADS 57 850 1948) thought well of 5% paraformaldehyde in talc or bentonite Parkhurst (ADS 27 662, 1933) described cases, 25% aqueous solution of aluminum chloride proving helpful.

ANHIDROSIS

Anhidrosis is the absence of sweating partial or absolute. It may be due to either insufficient function or deficiency destruction or absence of secretory apparatus. Anhidrosis is symptomatic in ichthyosis, ectodermal defects (q v) extensive psoriasis, scleroderma, morphea, and other cicatricial lesions, including roentgen dermatitis in avitaminosis A, dehydration and atropine poisoning in various disorders of the nervous system (see Hyperhidrosis) and in contact dermatitis due to astringent chemicals, including formaldehyde and other agents capable of producing squamous dermatitis. The review by Shelley et al. (Med 29 195 1950) was comprehensive.

Localized lesions in the cord, medulla and pons and of the sympathetic system can cause circumscribed loss of thermoregulatory sweating (List and Peet: ANeurol 40 27 1938 42 1098 1939) Typical areas of anhidrosis occur after various forms of sympathectomy Postganglionic sweat fibers contained in gray rami communicantes supply the skin in segments roughly

corresponding to the sensory radicular innervation. The location of lesions in the sympathetic nervous system can be delineated by investigations of thermoregulatory sweating Anhidrosis occurred in cutaneous areas corresponding fairly closely to segmental levels at which sympathetic nerves were distributed in the spinal nerves in cases of sympathectomy studied by Roth (AmJPhysiol 119 393 1937) It involved the areas of skin supplied by the gray rami of each ganglion corresponding in the main to the areas of skin supplied by the homologous posterior root fibers.

In the effort to treat anhidrosis, sometimes no method of attack exists. In the generalized forms such as ichthyosis (q v) the best that can be hoped for is alleviation. The wearing of soft, warm clothing and the daily application of bland soothing lubricants such as petrolatum and hydrous wool fat will serve to protect the skin. Vitamin A and perhaps thyroid or estrogenic substances may be indicated.

THERMOGENIC ANHIDROSIS AND TROPICAL ANHIDROTIC ASTHENIA

Acquired anhidrosis was generalized in a man who, with paratyphoid fever suffered exfoliative dermatitis and associated alopecia (Fog: J 107 2040, 1946) Pilocarpine induced salivation but no sweat; and histologic study revealed cystic degeneration of about half the sweat gland. Generalized acquired anhidrosis interested Engelhardt and Melvin (AmJMedSci 210: 323, 1945) whose patient was intolerant of heat for 13 years and did not sweat even when heated to a rectal temperature of 105 F Minor's test showed sweating only in axillary sternal, and perianal regions, and histologically the sweat glands were trophic.

Tropical Anhidrotic Asthenia was described by Allen and O'Brien (MJ Austral 2 335 1944) of whose 22 cases, 18 showed miliaria rubra due to corneous obstruction of the sweat ducts. This was the cause, apparently of the failure of the sweat mechanism in the desert described by Wolkin et al. (J 124: 478 1944) and atypical heat stroke by Blank (J 124 1152 1944) See also Laddell et al. (Lancet 2: 491, 527 1944) The subjects were soldiers enduring desert maneuvers who would manifest increased sweating of the neck and face and anhidrosis and cutis anserina below the neck level. Weakness, dizziness, headache, tremor and subjective warmth followed, and the skin became warm and dry from the neck down. Hyperpyrexia and coma did not develop nor was there increase of pulse or respiration. Administration of salt was ineffective, and pilocarpine and Mecholyl would not induce sweating until the patient had recovered by resting in a cool climate. The disorder came on rather suddenly was preceded by hyperhidrosis for a few days or weeks, and responded promptly to a change of the conditions under which it appeared.

The syndrome differs from heat stroke, which is characterized by collapse delirium irritability and visual disturbances, preceded by nausea and vomiting beginning often with dramatic suddenness, and manifested objectively by psychic changes, hot dry skin, hyperpyrexia, rapid pulse and increased depth of respiration. It differs also from heat exhaustion, which is manifested by headache drowsiness, extreme weakness, visual disturbances, vomiting vertigo and inability to walk, with cramps of limb and abdominal muscles, cold and clammy skin, dilated pupils, fast pulse diminished blood pressure and temperature not increased or increased only slightly

In atypical heat stroke the face became flushed when hot drinks were imbibed, and the skin showed a scaly fine, papular rash on the extensor aspects of the extremities, superficial circinate areas of erythema with white scaling and mild pruritus. The patients of Novy (J 125 738 1944) developed this disorder in a hot humid climate It is dangerous in these cases to withhold salt (Miller: J 124 1152, 1944) The disorder can simulate a psychogenic one (Strauch: ADS 53 70 1946) but when Mecholyl is given only the head and hands sweat.

The sweat retention syndrome may be divided into 2 groups of cases (Sulzberger et al. JID 9 221, 1947) both showing signs and symptoms due to failure of sensible perspiration, one due to plugging of glandular orifices, the other due to atrophy of the ducts. These phenomena may occur in atopic dermatitis, lichenoid quinacrine eruption and other conditions.

A significant degree of sweat retention is frequently present in the common eczematous dermatoses and psoriasis, according to Cormia and Kuykendall (AD 71: 425, 1955) who measured retention and found correlation between its degree and the extent to which heat aggravated the eruption. Sweat retention was evidently due in their cases to obstruction in the upper epidermal portion of the sweat ducts, for the dermal portion showed no abnormality other than dilation, and the glands appeared functional despite the obstruction. Hypotheses concerned with the significance of sweat resorption resulting from obstruction and retention were extensively discussed by Sulzberger and Herrmann (The Clinical Significance of Disturbances in the Delivery of Sweat, Thomas, 1955). See Miliaria and Sudamina.

Miliaria, sudamina, and prickly heat were used as synonymous by Sulzberger and Emik (JID 7 53; 61 1946) Their studies concerned military personnel on Guam, two-thirds of whom developed the disorder within a 7 months' residence there. Focal hyperkeratosis at the follicular orifices and diminished sweating in the affected regions were demonstrated. The pathologic changes of the sudoral apparatus were interpreted as paralleling that of the sebaceous apparatus in acne vulgaris.

Prickly heat and tropical anhidrotic asthenia are different manifestations of the same fundamental process (Sulzberger et al.: JID 7 153 1946) Miliaria rubra represents the acute phase of sweat gland occlusion, with tiny, glistening papules surrounded by red areolas anhidrosis represents the chronic phase with occlusion, hyperkeratosis, and disappearance of inflammation (O'Brien: BJD 59 125 1947) If lanolin is smeared on the anhidrotic patient and he exercises the greased area will sweat and no vesicles will arise there. The sweat glands are not atrophic or inactive but sweat is resorbed as it is formed. The sweat duct dilates and later ruptures close to the level of the keratinous obstruction. Fox (ADS 60 173 1949) reviewed the subject fully and confirmed the histologic findings of Allen and O'Brien that keratinous plugging of sweat orifices is characteristic. The concentration of chloride in the sweat is high (Ladell: BMJ 1: 1358 1951)

In describing 38 cases, O'Brien (AIntM 81: 799 1948) noted the insidious onset, which may however be acute in prickly heat. Exercise in heat and sunshine produces excess fatigue with unusual sensations of heat, throbbing frontal headache giddiness, dyspnea, palpitation and, perhaps, itching The skin is objectively hot and tense and the trunk and limbs remain dry even though profuse sweating appears on the forehead and face during exercise After exercise, most or all of the covered areas, devoid of sweat are studded with deep white vesicles of 1 mm. or less diameter representative of the escape of sweat from blocked and ruptured sweat ducts. The patient is relieved after from half an hour to 3 hours in a cool place. The disease may last for several months before normal sweating is resumed.

The causes of sweat pore closure are manifold, and include staphylococcic infection, excessive use of soap, and defatting by solvents perhaps edema of the stratum corneum, *whatever it may be due to, can cause temporary* pore closure a d so miliaria crystallina (O'Brien: JID 15 95; 102; 134 141, 1950) Sweat retention anhidrosis was produced locally by Shelley et al. (JID 11: 75, 1948) and Shelley and Horvath (JID 14: 9; 193, Dec 16 53 1951) by injuring the skin in various ways such as by iontophoresis, maceration, adhesive tape phenol, ultraviolet heat and cold. Any superficial injury it seems, which stops up the pores can cause this manifestation of nonspecific epidermal damage with obstructive, hyperkeratotic plugging of sweat gland orifices. When obstructed glands were stimulated, miliaria appeared. See Hyman, Lobitz, Shelley and Hurley and Herrmann and Sulzberger (ADS 66 145 ff., 193)

Producing eccrine sweat retention experimentally by aluminum chloride applications, Shelley (JID 22 267 1954) studied the glycogen levels of the tubular secretory cells as an index of secretory activity Keratotic plugging of the pore results in minimum glandular activity unless rupture of the duct occurs. If rupture occurs, then sweating can be maintained at normal rates as evidenced by the rapid disappearance of glycogen from the secretory cells of the tubules. Experimental injury of the orifices of apocrine duct was accomplished by Hurley and Shelley (JID 22 397 1954) but no clinical changes resulted. Nitric acid applications or electrodesiccation induced keratotic plugging of the duct orifices, cystic dilation of the ducts and tubules and flattening of the lining cells.

Treatment with salicylic acid in alcohol, causing desquamation, followed by applications of animal fat, is helpful. Best response is obtained if the patient is removed from the climatic conditions which cause his trouble. Improper utilization of vitamin A was determined to be present in a patient of Lobitz and Kierland (ADS 64 411 1951) Vitamin C might help See Miliaria

SUDAMINA AND MILIARIA

Sudamina is the name given to a noninflammatory brief but abundant eruption of pinpoint to pinhead-sized, superficial, thin-walled, translucent, pearl like vesicles representative of sweat duct obstruction. The lesions are whitish and closely set, but they do not coalesce. Their clear content is acidic, in contrast with the alkaline content of the vesicles of miliaria rubra, according to Jadassohn, quoted by Becker and Obermayer (Modern Dermatology and Syphilology Lippincott, 1940 p 507)

Miliaria is an acute, inflammatory disorder of the coil glands, characterized by the sudden appearance of numerous pinpoint to pinhead-sized papules and vesicles, accompanied by sensations of itching and burning The malady usually develops in hot weather and is especially common in tropical countries. Individuals who habitually sweat profusely are particularly susceptible to the affection. The lesions may be papular papulovesicular or vesicular rarely pustular and, while they may be closely crowded together they never coalesce Their content is alkaline. In "miliaria rubra" they are at first surrounded by pinkish areolae, but later they become pale and whitish or yellowish white in color "miliaria alba." Ultimately the papules regress, and the vesicles dry and undergo desquamation. Rarely a few become infected with staphylococci and form minute abscesses. The eruption may be of more or less generalized distribution, but usually it is limited to the covered parts of the body The lesions develop quickly and disappear as a rule in the course of a few hours or days. Medicinal irritation or progressive intertriginous dermatitis may ensue.

Exposure to excessive heat, particularly moist heat, is the exciting cause of the disorder Infancy obesity debility overclothing and a tendency to hype hidrosis are predisposing factors. Indulgence in alcohol rend rs one especially susceptible. Pollitzer (JCutD 11: 50 1893) recognized cystic dilation of sweat d cts due to occlusion of their orifices. Robinson (JCutD 3 302, 1884) observed inflammation of the epidermis in the vicinity of the coil gland pores. Compare Intertrigo; see Tropical anhidrotic asthenia. In cases of Leibmann (MedKlin 33 1368 1937), a fine pustular eruption followed the exanthem of sca latina. Exposure to ultraviolet light is frequently followed by miliaria alba because of the blockage of sweat pores (Thomson: JPhysiol 112: 22 31 1951)

The weather with respect especially to temperature and humidity correlations, was evidently concerned in the etiology of th condition, studies of Sams (SouthMJ 44: 140 1951) showed. The ill effects of warm, moist weather with low wind velocity were cumulative The incidence and severity of the disorder were correlated with climatic conditions likewise by H rns (JID 16: 97 1951), who established minimum air temperature and humidity conditions for the existence of the disease, and found that the higher these figures were, the more common and more severe prickly heat was. Miliaria is common in the personnel of submarine crews (Pugh: J 144: 220 1950)

Preventive measures consist in guardi g against exposure to excessive heat, the wearing of too much clothing, or the use f alcohol. Mild astringent lotions, such as dilute aqueous solutions of luminum acetate, permanganate resorcinol o alcohol, usually pro e helpful, particularly when thei use is supplemented by liberal applications of a bland dusting powde such as boric acid, zinc stearat o a mixture of 2% salicylic acid in equal parts of boric acid and starch. That the ction of bacteria is concerned is attested by the success of neomycin lotion compared with placebo control used i treating miliaria rubra by Lyons and Hunt (JID 4 647 1953)

Pustular Miliaria (Syringadenitis Suppurativa Tropicalis) sometimes represent parasitic infection of the sweat glands, especially of the f ce. It simulated iodide eruption in the Chinese patients of Reiss (JLabClinM 28: 1082, 1943), who found vit min C useful i treatment, large doses being required unless the hot weathe subsided and perspiration decreased (Reiss J 145: 755, 1951) The value of vit min C in generous dosage was con firmed by Stern (J 146: 175 1951) with respect to miliaria, sudamina and "lichen tropicus in troops stationed in the constantly hot, humid South P cific islands. The disease resembles folliculitis (Lobitz J 148: 1097 195_) It appears more often in summer months but may occur at any time. It is more common i dults than in children. Its pruritus and exacerbations parallel the intensity of sweating Individual lesions a e distinct discrete, superficial, and not associated with hairs. A da k dot sometimes visible in a pustule represents a hype keratotic plug in a sweat pore the cont t of which is white nd generally sterile according to Lobit although I m con inced that st phylococci may be significant in som cases (compare Rosacea lik follic litis p. 279)

In treatment the voidance of sweating would be desirable. Vitamin C, 500 mg. t.i.d., may be given. Topical antiseptics, such as "% salicyl c acid in 5% ammoniated mercury oi tment, or 0.5% chloramphenicol in Vioform Cream may be indicated. X-ray therapy seems not to help.



Fig. 1911.—Pustular miliaria: lesions of flexural aspect of forearm at site of previous contact dermatitis from paint. (Lobitz J 148 1097 1952.)



Fig. 1912.—Pustular miliaria close-up showing (1) hyperkeratotic plug on top of pustule and (2) another lesion i a different stage of evolution. (Dr Walter C. Lobitz, Jr)



Fig. 1913.—Pustul miliaria: close-up of scrotal lesion showing absence f involvement of hair follicles, discreteness of pustules, and presence of hyperkeratotic plugs in roof of pustules. (Dr W lter C Lobitz, J)



Fig. 1014.—Pustular miliaria hyperkeratotic plug surmounts intraepidermal abscess; note duct fragment just beneath pustule. (Dr Walter C. Lobitz, J)

PECULIARITIES OF COLOR AND COMPOSITION OF SWEAT

Chromhidrosis is an affection characterized by the excretion of colored sweat. True chromhidrosis is an extremely rare disorder Pseudochromhidrosis is caused by the presence of chromatogenous microorganisms or various tinctorial substances on the surface of the skin (see Trichomycosis flava, nigra, rubra) The discoloration is usually brownish, grayish, bluish or violaceous. The secretion commonly collects slowly on the skin and imparts to the affected areas a greasy powdery appearance, such as might result from applying lead pencil dust to a seborrheal surface (Mitchell PhilaMJ 1 117 1898) The pigment is mixed with grease though only slightly soluble in water it can be removed readily with the aid of benzine or ether

A Negro with bluish axillary sweat and a woman with black sweat of the face were studied by Shelley and Hurley (JID 19: 763 1953) who judged the secretion to be of apocrine origin. Most cases of idiopathic colored sweat are cases of colored apocrine sweat, yellow sweat being the commonest of these rare instances. Reviewing the subject and presenting observations on 12 patients, Shelley and Hurley (ADS 69 449 1954) described intrinsic, localized chromhidrosis as an abnormality in which colored apocrine sweat is produced. While it may occur anywhere, its presence indicates the existence of underlying apocrine glands. The colored sweat may be yellow green, blue, brown or black, and it is discharged in response to emotional stimuli, epinephrine or mechanical stimulation of the myoepithelium. Yellow, blue and green sweats fluoresce yellow in Wood's light, but black sweat does not. Granules of lipofuscin pigments are present in both normal and chromhidrotic apocrine glands, the difference being in the quantity so that histologic diagnosis is possible. The color of the sweat in chromhidrosis is evidently due to various amounts of lipofuscin in various stages of oxidation, the greater th xidation, the darker the hue. In the case of Heidingsfeld (J 39 1519 1902) the disorder was pparently an anomaly of pigmentation rathe than an alteration of glandular secretion.

Hematidrosis (Bloody Sweat) is an extremely rare disorder characterized by excretion of blood or blood pigment through the coil glands. When it does occur it is usually manifestation of purpura. The majority of the reported examples ha e occurred in the ewborn and in highly emotional o hysterical subjects. The disorder may involve limited rea on the face, ears, umbilicus or limbs, and the discharge may be preceded or accompanied by pain of a neuralgic character At times the condition is associated with othe

bleeding stigmas, vicarious menstruation and similar conditions. Scott (BMJ 1 52, 1918) reported an interesting case. Török found red cells in the lumen of a coil gland, and it is possible, as suggested by Crocker (Diseases of the Skin, Blakiston, 1905, p. 1003), who gave an extensive bibliography on chromhidrosis, that the condition is secondary to purpura of the sweat coils.

Lymphathidrosis, to coin a word, is appropriate to designate the singular case of "weeping of lymph through the unbroken skin," described by Borman (AD 71: 495, 1955) see Lymphangioma (p. 1129)

Galacthidrosis.—The sweating of milk has been alleged to have occurred. Newborn babies have been known to secrete milk from their mammae, influenced by pregnancy hormones during gestation; this lasts only a few days. Galacthidrosis is nonexistent, according to Hebra (Diseases of the Skin, New Sydenham Soc., London, 1866, vol. 1, p. 96)

Urhidrosis denotes the excretion of sweat containing abnormal quantities of urinous elements, particularly sodium chloride and urea. It may occur in uremia (Bittner and Robbers KlinWchr 14: 372, 1935) After evaporation of the fluid constituents, the excreted material appears on the surface as a hoarfrost-like coating, consisting of whitish crystals and irregular powdery masses.

Phosphorhidrosis is extremely rare. Its occurrence has been noted in malaria, cancer of the breast, pulmonary tuberculosis, and following the ingestion of fish. It is possible that the phosphorescence has been due to photobacteria (Beyerinck: BMJ Supp. Jan. 1, 1891 quoted by Crocker)

See Pigmentation, discolorations Foot (DublinQuartJMSc 41 64, 1866), chromhidrosis Clapton (MTimes&Gaz 1 658, 1868), green occupational copper stain; Greig (EdinMJ 37 321 1930) melanhidrosis Mayr (HandbHuG, Springer 13: 1 1, 1932) diseases of sweat glands QMN (J 100, 136, 1932) yellow sweat, Bamberger (DWchn 109 866, 1939) perianal, orange, review and classification, Murray (ADS 41: 278 1940), yellow tears and sweat stopped when face powder was discontinued, Yoshihiro and Araki (abs ADS 45 166, 1942) red sweat Hayden (AnnAllergy 4 1 372, 1946) blue discoloration came off on washcloth, perhaps due to excretion of indigo in colorless state oxidized in air QMN (J 142 451 1950) blue QMN (J 146 222, 1951) physician with red axillary sweat.

NEW GROWTHS INVOLVING THE GLANDS OF THE SKIN

See Sebaceous cyst Milium Sebaceous and sudoral carcinomas Sweat gland tumors Apocrine cysts of the scalp Pilosebaceous adenomas Basal cell carcinoma, pathology

DISEASES AFFECTING THE MUCOSAE ADJOINING THE SKIN

Diseases of Mucosae constitute as broad a subject as diseases of skin. Mucous membranes adjoining the skin may be considered, for purposes of dermatologic thought, as simply thin skin, modified by these conditioning features: (1) mucosae are more or less continuously wet; (2) they are covered with stratified squamous epithelium which normally does not produce a stratum corneum (3) they lack hairs, but do not necessarily lack sebaceous glands (see Fordyce's disease) (4) they lack sweat glands but, in the mouth particularly, they are provided with mucous glands and (5) mucosae are so located and arranged with respect to underlying structures that their hazards, contacts and parasites are somewhat different from analogous cutaneous ones.

Similarities of mucosal and cutaneous disorders are notable

Mucosal tissues are susceptible to mechanical, chemical and allergic disturbances.

Mucosal tissues may be superficially infected with transitory parasitism which leaves no trace or inoculated with the chancres of various infections, or deeply infected with ulceration which results in scar

Mucosal tissues are damaged, as the skin is, by systemic parasitism, such as syphilis, leprosy, tuberculosis and other systemic infections.

Mucosal tissues are altered by metabolic processes, including xanthoma avitaminoses and endocrinopathies much as the skin is.

Mucosal epidermis may be malformed, like that of the skin with, for example, ichthyosiform nevi; and mucosal mesodermal tissues are susceptible to hemangiomatous, neurofibromatous and other malformations.

Mucosal neoplasms include epidermoid and glandular carcinomas and sarcomatous lesions, and these may be primary or secondary

Mucous Membranes Adjoining the Skin are those of the following regions oral penile, vulvar and vaginal anal nasal and conjunctival. While emphasis here is largely on oral aspects of mucosal disease I will tabulate the affections described elsewhere in this volume in which more or less conspicuous or frequent mucosal involvement may occur

PENILE MUCOSA

Calculus	Gangrene, infectious	Lymphogranuloma inguinale
Carcinoma	Gonorrhea	Moniliasis
Chancroid	Herpes simplex	Reiter's disease
Chigger bites	Impetigo	Scabies
Condyloma acuminatum	Leukoplakia	Syphilis
Dermatitis venenata	Lichen planus	Verruca
Erythroplakia	Lichen sclerosus	Vincent's infection

VULVAR AND VAGINAL MUCOSAE

Acanthosis nigricans	Hidradenoma	Oxyuriasis
Avitaminosis	Kraurosis	Pellagra
Carcinoma	Leukoplakia	Pemphigus
Dermatitis venenata	Lichen planus	Pruritus vulvae
Endometrioma	Lichen sclerosus	Syphilis
Erythema multiforme	Lichen simple	Trichomonad infestation
Herpes simplex	Lymphogranuloma inguinale	Ulcus vulvae acutum
Hidrosadenitis	Moniliasis	Verruca

ANAL MUCOSA

Acanthosis nigricans	Hidrosadenitis	Oxyuriasis
Amebiasis	Leukoplakia	Pruritus ani
Carcinoma	Lichen planus	Syphilis
Dermatitis medicamentosa	Lichen simplex	Tinea
Dermatitis venenata	Lymphogranuloma venereum	Tuberculosis cutis orificialis
Dermoid fistulas and sinuses	Moniliasis	Verruca

NASAL MUCOSA

Dermatitis medicamentosa	Leprosy	Streptococcic fissure
Dermoid fistula of nose	Myiasis	Syphilis
Diphtheria	Myriapod infestation	Telangiectasis
Folliculitis narium perforans	Ocular pemphigus	Tuberculosis
Furunculosis of vibrissae	Purpura	Verruca
Hirudiniasis	Rhinosporidiosis	Yaws, gangosa
Leishmaniasis	Scurvy	

CONJUNCTIVAL AND OCULAR MUCOSAE

Albinism	Gonorrheal dermatoses	Parinaud's disease
Ascariasis	Helminthiasis	Pemphigus, ocular
Atopic dermatitis	Hemangioma	Pinguecula in xanthomatosis
Avitaminosis	Herpes zoster	Purpura
Carcinoma	Ichthyosis	Rhinosporidiosis
Caterpillar dermatitis	Jaundice, pruritus in	Rosacea
Congenital ectodermal defect	Leprosy	Sarcoid
Dermatitis medicamentosa	Lichen planus	Smallpox
Dermatitis venenata	Lupus vulgaris	Sycosis, blepharitis in
Diphtheria	Measles	Syphilis
Eruptive fever with stomatitis	Melanoma	Tuberculosis
Erythema multiforme	Myiasis	Tularemia
	Ochronosis	Xeroderma pigmentosum
	Onchocerciasis	

Eyelids provide 3 regions of dermatological interest the external skin, the lid margins, and the conjunctivae. These are so close together that disease of one is likely to affect the others. Described elsewhere in this volume are the following diseases in which involvement of the eyelids occurs:

Alopecia areata	Exfoliative dermatiti	Sparganosis
Avitaminosis	Indelible pencil injury	Sporotrichosis
Blepharochalasis	Keratosis senilis	Stye
Carcinoma	Milium	Syphilis
Chalazion	Molluscum contagiosum	Tinea of lashes
Dermatitis medicamentosa	Myxedema	Trauma, hematoma
Dermatiti venenata	Phthiriasis	Trichiasis
Distichiasis	Purpura	Trichiniasis
Epithelioma ade oides cysticum	Rosacea	Tuberculosis lupus vulgaris
Eruptive stomatitis	Sebaceous cyst	Urticaria
Erysipelas	Seborrheic dermatitis	Wart
	Seborrheic keratosis	Xanthoma

ORAL MUCOSAE

Disturbances may be classed by location and by type and descriptions of oral mucosal lesions may be ordered accordingly with descriptions of each type of lesion in each location.

LOCATION AFFECTED	TYPE OF LESION
Mouth, in entirety or in part	Physical and Chemical Injuries
Teeth (ectodermal)	Parasitic Diseases
Lips, particularly	Symptomatic Mucosal Diseases
Gums, particularly	Pigmentary Disorders
Palate, particularly	Mucosal Diseases of Unknown Cause
Tongue, particularly	Malformations and Neoplasms

Teeth a ectodermal tructures of dermatologic concern in conditions described elsewhere congen tal ectodermal defect, focal infection galvanic lesions due to fillings, granulom p ogenicum sinus tracts of dental origin and congenital syphilis.

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Diagnosis of Diseases of the Mouth, Dental Items of Interest Pub. Co., 1935); Prinz and Greenbaum (Diseases of the Mouth, Lea & Febiger, 1935); Fox (PaMJ 38: 466, 1935), oral lesions of systemic disease; Witkowski (ZentrlblBakt 133: 334, 1935), correspondence of oral flora of newborn and vaginal flora; Darlington and Lefkowitz (AmJClinPath 6: 336, 1936) 1,000 surgical pathologic specimens from the mouth; Conroe (AmJMedSci 194, 441, 1937) the tongue in internal medicine; Hertzler (Surgical Pathology of the Mouth and Jaws, Lippincott, 1938); Ruppe (PresseMéd 46: 1484, 1938) stomatitis, review and bibliography Loveman (KyMJ 36: 569, 1938), elementary stomatology, Padgett (Surgical Diseases of the Mouth and Jaws, Saunders, 1938); Miller (Textbook on Periodontia, Blakiston, 1938 [p. 173, Webb on electro-surgical treatment of pyorrhea]) Figi (AnnOtol 48 81, 1939) elementary stomatology; Kennedy (Pract 143: 572, 1939) tongue; White (N WMed 38 431 1939) brief review; Parsons (ADisChild 15: 42, 1940), stomatitis in children. McCrea (Diseases of the Urethra and Penis, Wood, 1940) Kumer (AfDuS 182 69, 1941) ulcerative lesions, McCarthy (J 116 16, 1941) 2,300 cases; Jeghers (NEngJM 227: 221, 1942) tongue in nutritional deficiency bibliography, Mann et al. (Atlas of Dental and Oral Pathology, Amer Dental Assn., 1944) Army Dental Corps material; Parks (AmJObGyn 49: 396, 1946), similarities of oral and vulvar lesions, Krantwell et al. (ActaMScand 123 297 1945), stomatitis, 1,500 cases, illustrated Burket (Oral Medicine, Diagnosis, Treatment, Lippincott, 1946); Miller (Oral Diagnosis and Treatment, Blakiston, 1946) Busby (MissouriDoctor 24: 180 1946) local and systemic conditions; Fürstenberg (J 136: 1, 1948), salivary gland diseases QMN (J 138 934, 1948) bleeding gums Dietz (Millbourg 107: 178, 1950) oral ulcers; Tomaszewski (BDJ 1: 117 1951) the tongue in Wood light, fluorescence often absent in avitaminotic atrophy; Schaefer (OralSurg 4 1237, 1951), clinical pathology of tongue, Thoma (Oral Pathology Mosby, 1954, 1536 pp 1594 illust.) Duke-Elder (Text Book of Ophthalmology Mosby vol. 5, 1952), eyelids Hamsler and Schour (Atlas of the Mouth and Adjacent Parts, Amer Dental Assn.); McCarthy and McCarthy (NEngJM 250 403, 1954) statistics of diagnoses in 4733 cases of oral mucosal disease.

PHYSICAL AND CHEMICAL INJURIES OF THE MOUTH

Trauma.—Lesions such as cuts, fractures or gunshot wounds, and foreign bodies, including bones of fish and the like, are merely mentioned here

Cheilitis Due to Sucking the lower lip was described by Oppenheim and Fessler (AnndeD 6: 496 1935)

Pressure Sores of the lips may follow manipulations within the mouth by some dentists who lean on the lip instead of the teeth Pressure sores are particularly likely to follow work done during nerve block anesthesia, when the patient is not alert to defend himself. They may result from ill fitting prostheses and fillings, from malformations or distortions of the jaws or teeth, from rough edges or carious lesions or from pipe stems and other foreign bodies.

BEDNAR'S APHTHAE are excoriations occurring generally symmetrically on the sides of the rear of the hard palate over the pterygoid plates. They may arise from thumb-sucking from introducing foreign objects into the mouth such as lollipops, or from scalds. They heal in due time when the provocation has ceased. White petrolatum may be applied repeatedly as a protective. The lesion is most often seen in infancy when sucking is extensively engaged in. Monilia or bacteria complicate the disturbance Palatine trauma due to aberrant sexual practices produced a curious lesion observed by Rattner (ADS 60 694 1949)

Cotton Roll Gingivitis is the popular name for gingival damage which results from applying dry absorbent pads to the gums and pulling them away without first moistening them, with the result that epidermis adheres to the pad and is torn off. After 2 to 5 days of soreness, epithelization succeeds in re-covering the denuded mucosa unless healing is interrupted by further trauma parasites, or irritating medicinal agents.

Ulceration of the Frenum of the tongue may result from severe coughing especially whooping cough. It is a purely mechanical lesion unless it becomes secondarily infected. In tuberculosis it may be inoculated with the bacilli from the sputum.

Suction Hypertrophy of the Mucous Glands of the Palate is a disturbance due to suction and hypertrophy induced by the wearing of an upper plate or by smoking a pipe The midline region of the central and posterior thirds of the hard palate is the region where one sees a rhomboidal, bosselated group of smooth pinkish hemispheric nodules each being 1 or 2 mm. in diameter They are asymptomatic. They require no treatment, as a rule They may induce cancerophobia. See Orr (BJD 42: 436 1930) Ronchese (ADS 36 1222, 1937); Tappeiner (AfDuS 181 173 1940); Cummer (J 132 493 1946)

Malocclusion and its effects on the oral mucosae were the subject of an interesting study by Van Studdiford (ADS 67 546 1953) who called attention to fissures at the angles of the mouth resulting from a deep bite. He pointed out that all the teeth are necessary and that prosthetic needs should receive prompt and effectual attention.

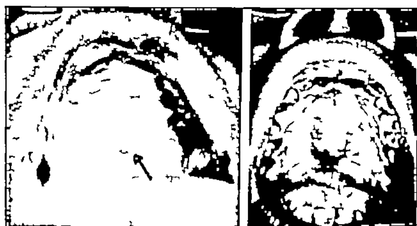


Fig 1915.—Swelling of mucous gland orifices and inflammatory leukoplakia of the palate of a smoker (Ronchese: ADS 36: 1222, 1937.)

Fig. 1916.—Lesions like those shown in Fig. 1915, in woman who totally abstained from tobacco. Note also t rus palatinus. (Dr F Ronchese.)



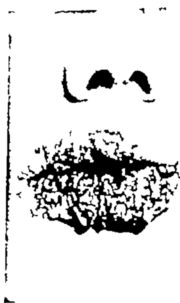


Fig 1917.—Hypertrophy f the mucous glands of the palat Such condition may result from suction due t an ill-fitting denture (Hayes, Clinical Diagnosis of Diseases of the Mouth, Dental Items f Interest Publishing Company Inc 1935.)

Fig. 1918.—Cheilitis such as may be caused by contacts t irritation from lipstick, dentifrice or medicines pplied, with bact rial ctivity superadded. (Dr W Herbert Dress.)

Burns of the lips and mouth are commonplace generally resulting from taking food while it is too hot occasionally from putting the wrong end of a cigarette into the mouth Therapeutic burns are performed for the purpose of destroying tissues, such as leukoplakia. Burns within the mouth may range from first to third degree They heal promptly if the mouth is simply kept clean and if the mucosa is not irritated by medicinal agents. During the healing of wounds made with the cautery the teeth should be kept brushed. Sodium perborate a teaspoonful to the glass of water is a useful mouthwash

but it is not tolerated by some persons, who do better with physiologic salt solution. The middle of the upper lip of a baby may be scaly from injury with spoonfuls of hot food.

ELECTRIC BURNS of the mouth are not extremely rare in little children (Oppikofer SchweizMWchn 69 1197, 1939) usually from putting plugs and wires into their mouths (Tummers abs J 143 1214 1950) The injury may be of any degree of severity possibly productive of speech defect and requiring plastic surgery for repair

Actinic Cheilitis occurs in the summertime as a rule affecting the person whose integument is sensitive to the sun s rays. The lips are swollen, sometimes considerably and the vermilion surface especially of the lower lip is scaly fissured, and more or less crusted. This is relieved by staying indoors or wearing a broad-brimmed hat and a thick layer of zinc paste as a sun screen (Ayres J 81 1183 1923) Gougerot (BaoefrancD 43 1592, 1930) noted that susceptibility exists from a youthful age and is sometimes familial, and that vulnerability is made manifest with swelling unsightliness and pain only as a result of exposure to the sun. He was undecided as to whether sensitivity or photosensitization is to blame. It is my observation that some individuals are simply not built for exposure to much sunshine just as some are not designed for weight lifting Their integuments are thin, and the sun s rays damage them. In this regard they are different from the more fortunate

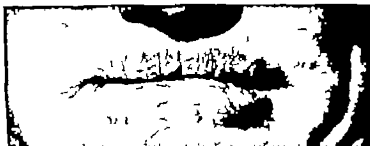


Fig 1919—Actinic cheilitis.

majority They are not sufferers from contact eczema, a common cause of exfoliative cheilitis, unless ill-chosen medicines are applied to their damaged tissues. They need not especially fear carcinoma, for they may or may not be affected with keratoses or neoplastic leukoplakia but it is common for the tendency to have keratoses and the tendency to be sun-sensitive to occur in the same individual

Actinic cheilitis is an occupational hazard of welders (Vernon J 140: 1333, 1949) See Sunburn.

Roentgen and Radium Injuries may occur within the mouth. Damage of the lip is a price one perhaps willingly pays for cure of carcinoma. One may excise the distressingly tender and sensitive atrophic and telangiectatic, sometimes ulcerated tissue and so give immediate relief. Xerostomia from roentgen treatment of lesions of the face is sometimes seen (Greenbaum and Tumen J 107 1297 1936) Roentgen injuries of teeth were discussed by Regato (AmJRoentg 42: 404 1939) Heavy-dosage technic typically produces destruction of the epithelium within the mouth on the treated side epitheliitis, as it is called. This is characterized by scarlet redness, vesiculation and flaky soggy exfoliation. See Gamma ray treatment (p. 1230)

Galvanic Burns of the mucous membrane were described by Lain (ADS 25 21 1932; J 100: 717 1933) as resulting from the electric current which passes through saliva and oral tissues, serving as electrolyte, when fillings of dissimilar metals are present in one mouth With the metals in common use by dentists, the current is a small one and its ability to dissociate the salivary solution into hydrochloric acid at the cathode and sodium hydroxide at the anode

is small. That such currents exist is indubitable. That they are consequential is debated. A new amalgam filling has a curious electric taste but, when the mercury and silver become settled in their relationship this disappears. Acid or alkali could collect in noxious concentration only if the contact zone were quiescent and unwashed by saliva galvanic lesions are almost inconceivable in a wet mouth and in a dry one they would be hard to distinguish from avitaminotic leukoplakia.

Hollander (J 99 353 1932) reported 1 case of galvanic leukoplakia and of decubital ulcer in which healing took place after the removal of fillings made of dissimilar metals. Lain described irritation of the tongue, gingivitis, patches of congestion erosion, ulcer and leukoplakia resulting from such currents. The tongue was swollen and irritable in the case of Hollander et al. (J 100: 1029 1933)

Granowsky (DWchn 98 806, 1934) reported several cases allegedly associated with the use of musical instruments. Rattner (ADS 31: 701, 1935) saw glossitis cured by the removal of amalgam fillings from a mouth also containing gold. Solomon et al. (ats J 111 2306 1938) tested the currents in artificial and actual saliva, and discovered that film formation occurs, so that the expected electric current probably does not normally



Fig. 1920.—Dental lesions following roentgen therapy of cancer of oropharyngeal tissues (Hagato AmJRoentg 41 404, 1939.)

flow in the mouth. They concluded that no causal connection exists between meter readings obtained between metallic restorations and whatever tissue alteration are also present. I have seen teeth, time and money wasted on dental work induced by the theoretic consideration. Such alteration gives no relief in burning tongue is a practical means of attacking oral disorders it is among the last resorts. Commonly enough fillings ought to be removed, when their rough edges or infection beneath them justify their removal and removal is followed by relief of symptoms. One could diminish the possibility of galvanic damage greatly by having the subject drink generous amounts of water so that the saliva would flow freely

That the current itself and its electrolytic effect are not the prime agents of harm was the point of view of Lain (ADS 41 295 1940) Rather he suggested, the current may act cataphoretically by introducing metallic ions into the tissues adjacent to the fillings. He demonstrated that amalgam in these cases becomes unusually shiny and that the tissues contain detectable quantities of metal The lesions, then, he believed, are true tin, nickel or mercury dermatitis. These forms of inflammatory stomatitis are considered under Dermatitis venenata (q v) The question of allergy versus electrogalvanism was discussed by Hazel et al (ADS 61 781 1950) I have failed to identify a case in my practice

Chemical Injuries of the mouth may be suffered from acids, alkalies and caustics, such as copper sulfate phenol, iodine, and other agents. The extent of the injury primarily determines its significance Ulcers heal readily within the oral cavity if the individual survives his poisoning Damage done to the pharynx and esophagus is important, for perforation leads to death, and cicatrization leads to serious difficulty Emergency treatment consists in generous lavage with water using weak dilutions of vinegar for lye or bicarbonate of soda for acids—one depends mainly on aqueous lavage.

Mercuric chloride tablets are coagulant when they touch the mucosa, aside from the toxic effect when absorbed (see pp 181 450, 838 1412)

Chemical damage is often directly due to medicines, such as chromic acid and silver nitrate, acting as caustics. Lemon juice habitually imbibed is capable of dissolving off the enamel and producing extensive dental damage (Stafne and Lovestedt PSMMC 22 81 1947) So is iron (James and Parfitt BMJ 2 1252, 1953) See also Stomatitis venenata below

Tobacco Stomatitis is a form of chemical injury Actual hypersensitivity is apparently exceedingly rare. In the ordinary irritation, the mucosa is red and injected, and the mucous glands pour out excessive amounts of secretion, which leads to pharyngeal droppings, hawking and cough. It is conceivable that benefit may result from changing the brand of cigarette to one using diethylene glycol instead of glycerol better is to stop tobacco.

The tarry distillate of the smoldering woody stuff is keratolytic, as salicylic acid is, and the mouths of some persons become the seat of extensive inflammatory, exfoliating leukoplakia. Distinct from neoplastic leukoplakia irritative leukoplakia fades gradually at the margin into unaffected tissue lacking a definitive border The combination of suction and irritation produced by smoke leads often to enlargement and minor inflammation of the mucous glands of the palate and the tissues about their orifices (see suction hypertrophy of mucous glands, p 1397)

Whatever neoplastic leukoplakia coexists in the irritated mouth is thickened and intensified by smoking It is commonplace to observe the cessation and disappearance of peeling of the buccal mucosa when smoking is completely discontinued. Individuals with fair and sun-sensitive skins are especially liable to tobacco injury of the mouth. The man with a red tint in his hair and actinic keratoses on his face would be wise to pass tobacco by

The importance of tobacco as a provocator of carcinoma of the mouth has not nearly sufficiently been stressed. There is no moral question involved in this fact. It is a plain truth, like the truth that a red-haired farmer in Kansas is likely to develop skin cancer by the time he reaches his seventies. The combination of constitutional predisposition with inciting instrumentality is necessary and I would not presume to deny an American citizen the privilege of encouraging his leukoplakia to develop into malignancy for he is a free agent and "the cause of cancer is not known"; but all in all I believe that the danger signal is a large and brilliantly red one

Tobacco does not need to be smoked to cause leukoplakia and cancer Cuds of chewing tobacco repeatedly applied to the buccal mucosa over a period of years, are equally effective.

What smoking does to lungs from the standpoint of carcinogenesis, is at present vociferously *sub judice*

Stomatitis Venenata (Contact Mucositis) —There is no substantial difference between hyperergic contact inflammation involving mucosae and dermatitis venenata (q v) Contact damage typically is variable in intensity in relation with the noxa and its application flares indicate contacts, and continuous disease indicates continuous or frequently repeated contact. Medicinal agents often irritate mucosae Oral manifestations of occupational origin were reviewed fully by Shour and Sarnat (J 120 1197 1942)

Cheilitis Venenata.—Toilet articles are usually at fault. Lipstick, cold cream, dentifrices, chewing gum and camphoraceous medicines are common causes. The lesion is likely to be manifest with swelling scaling oozing unsightliness

and discomfort, and its margin is a fading one rather than definitive as in lupus erythematosus. The process may be mild but persistent. Lips and face may be affected by sensitivity to the rubber of dentures. Lips may show mercurial dermatitis following the placing of an amalgam filling. Various dentifrices have been caught causing trouble and mouthwash, lipstick, perborate, orange peel, cinnamon oil, chewing gum and penicillin troches have been incriminated. Soap, shaving soap and aftershave lotions often irritate lips.

GINGIVITIS VENENATA.—The gums are swollen, possibly flaky and oozing, red, and excoriated, particularly at the vulnerable tips of the papillae. The teeth may be sore and the discommodation is perhaps so great that eating is almost impossible. Irritation in the mouth is always accompanied by salivation. It is seldom the gums alone are involved. The tongue is generally swollen, too, so that the teeth make pressure indentations. The common causes are dentifrices, mouthwashes and medicines. Vincent's infection may attack the damaged tissues. I have not in recent years identified a case of primary Vincent's disease, but I have seen much irritation of gums produced by therapy directed against alleged Vincent's disease.

STOMATITIS VENENATA.—While this affects a large proportion of the oral mucous membrane, or all of it, the tongue is generally considerably involved. The surface is redder than normal, is more or less swollen, and causes symptoms of sensitiveness, burning and tenderness. Flares occur when the contactant is of external source and is met only occasionally. As in skin, contactant injury may be caused by primary irritants or sensitizers. Foods are occasional sources of this trouble, especially chocolate, pecans, walnuts and salty popcorn. I have seen cheilitis due to oranges. Medicines of cough drops, nose drops, tonics, breath purifiers and whiteners of the teeth, along with synthetic chemicals of candies and flavorings, may be at fault.

In the mouth, the attachment of epithelium with mesoderm is not papillated, and epithelitis leads to ulceration. Vincent's organisms, probably always present as saprophytes, speedily take advantage of the situation and intensify the damage. On finding fusospirochetosis in smears, the average dentist applies potent chemicals to combat it and so enhances injury without getting rid of the underlying contactant cause. The volatile oils used by oral hygienists because of their pleasant fragrance are by no means rare provocators of mild or even severe stomatitis.

Lichenification seems not to occur in the mouth. Perhaps some leukoplakias are in fact the mucosal analogue of lichenification. Lichenification certainly is seen in anal and vulvar mucosae, but I have yet to identify it within the mouth. Bacterial complications of stomatitis venenata may lead to cellulitis, abscess or purulent cheilitis (Volkmann's type) or, if necrotizing, to noma. Vesicular oozing and crusting are common enough on the lips. Streptococcic complication of eczematous stomatitis may take the form of chronic redness, soreness, edema and excoriation affecting especially the lymphadenoid tissues of the tongue (lingual tonsillitis, q.v.) and the throat and perhaps the gums as of the tongue... Streptococci are regularly found on the sore tongue of pernicious anemia. Mycotic infections of the mouth are usually monilial.

The cure of this disorder depends basically on preclusion of something from the region, not on the application of medicines. The lips are comforted by cool, moist applications of 1:500 aluminum acetate on a bit of cotton, a pack which may be laid on top of a layer of petroleum jelly. In the mouth, physiologic saline solution is satisfactory as a frequent tepid lavage and no medicine at all works better than any other therapeutic agency. Some chronic cases prove difficult, particularly when the lips alone are affected. A scalp lotion may be to blame. Moistening the fingers with the tongue allows any chemical one has touched to reach the mucosa and investigation must be pursued much as in contact dermatitis.

Technic for patch testing mucosae has been described by the Goldmans (ADS 50: 79, 1944) and Farrington (JID 8: 59, 1947).

Elimination technic should be easy brush the teeth with baking soda rinse the mouth with saline solution use no other toilet article, leave off lipstick and quit chewing gum Secondary infection must be treated appropriately Many antibiotics are prone to cause stomatitis and must be used with care.

See Sutton (JAMA 71 358, 1911), cheilitis; Gaskill (JCutD 33 498, 1914), cheilitis exfoliativa, Templeton and Lunsford (ADS 25 430, 1932) "S.T.37" toothpaste, Rattner (J 106 2210 1936), denture material; Hecht et al. (J 112 1410, 1939), lipstick; Woodburne (JMich SMS 39: 467 1940) sodium perborate; Beinhauer (ADS 41, 191, 1940) dentifrice, in 1 case, thymol; Bowen (SouthMJ 31 104, 1941), allergic conjunctivitis, Miller (J 116 131, 1941) occupational, from cinnamon; Silvers (J 116 2257 1941), from chewing poison ivy Goldman (ADS 53 113, 1946) from penicillin mouthwash but not due to penicillin Putkonen (ActaD-V 26 316, 1946) lipstick; Goldman and Tronstein (JID 14 57 1950), penicillin toothpaste; Laubach et al. (J 152 404, 1953), synthetic cinnamon in toilet articles, Lupton (ADS 68 112, 1953), cheilitis from coffee Fisher and Tobin (J 151 996, 1953) "G-4" in dentifrice Schwartz (J 151 1431 1953) prophetic patch tests predicted intolerance f "G-4" dichlorophene Fisher (J 156 238, 1954) acrylic resin liquid monomer irritating, 4 cases, not the polymer which could be worn denture by persons allergic to monomer Harkness (BMJ 1; 1416, 1954) perlèche due to denture materials, patch test reaction sometimes delayed for 96 hours.



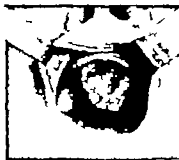


Fig 1921.—Filiform verrucae of tongue. (Dr John W Perkins)

Fig. 1922.—Papilloma of palate pedunculated, cauliflower like, warty tumor (Hayes Clinical Diagnosis of Diseases of the Mouth, Dental Items of Interest Publishing Company, Inc., 1936.)

PARASITIC DISEASES AFFECTING THE MUCOSAE

Specific Infections may affect mucosae either as primary infections originating in mucosal tissues or as systemic diseases with mucosal manifestations. Described elsewhere in the chapters on dermatoses due to various parasites, see the following diseases due to

Viruses Measles, Herpes simplex herpetic stomatitis Ulcus vulvae acutum Herpes zoster Foot and mouth disease Warts, affecting lip, tongue, anogenital mucosae Molluscum contagiosum affecting lid margins; Lymphogranuloma venereum

Rickettsiae Typhus and Rocky Mountain spotted fever petechiae;

Bacteria. Impetigo, spreading onto mucosae, Staphylococcic abscesses and cellulitis Erysipelas ; Scarlet fever; Gangrene of the face; Meningococcemia; Tularemia ; Glanders; Chancroid; Granuloma pyogenicum; Rhinoscleroma Anthrax; Diphtheria; Tuberculosis, primary and orificial Granuloma inguinale; Pinta; Yaws; Syphilis, primary secondary and lues latum, mucous patches, gummatous, congenital;

Fungi Tinea, perianal; Blastomycosis; Coccidioidomycosis; Moniliasis thrush, vulvovaginal, perlèche; Torulosis; Rhinosporidiosis; Actinomycosis Sporotrichosis Histoplasmosis; Cephalosporiosis;

Animal Parasites Amebiasis; Trichomoniasis; Leishmaniasis Onchocerciasis, Ascariasis and Oxyuriasis causing pruritus ani; Onchocerciasis, causing conjunctivitis and blindness Dirofilariasis; Caterpillar dermatitis affecting conjunctivae ; Myiasis of sinuses.

Warts of the mucous membranes are not consequentially different from filiform and ordinary warts. They occur on the lips or tongue occasionally on the buccal mucosa, having been inoculated, generally by biting verrucae vulgares on the patient s finger Warts, being inoculable can be transmitted by sexual activity They may luxuriate amazingly in the warmth and moisture

of the anogenital region. Podophyllin is effective in the treatment of most area warts (q v) but in and about the mouth the cautery with local anesthesia is to be preferred.

VERRUCOUS PAPILLOMATOSIS OF THE MOUTH.—Warty vegetations simulating the luxuriant type of growth occasionally seen about the vulva and anus were observed in 3 patients by Howarth (Laryng 50: 33 1935) Every effort to rid the patients of their lesions resulted in failure. A similarly resistant case involving the tongue and palate of a woman 50 years old was presented by Anderson (ADS 36 1307 1937) Hayes (19[illegible]) depicted such a lesion a coral like vegetation springing from the roof of the mouth. These lesions are distinct from warts of the ordinary type and from vegetating epidermal [illegible]plasia. Some cases of this kind are ichthyosiform nevi (q v)

How to treat hypertrophic papillomas successfully remains problematic; there is a likelihood of overtreating them so that the patient is worse disabled than he needs to be

Herpetic Stomatitis (Herpangina) —See Herpes simplex (p. 815)

Plaut-Vincent's Disease— Trench mouth" is an acute ulcerative infection of the mucous membranes attributed to a combination of fusiform bacillus and spirochete (Plaut DMedWehn 20 920 1894 Vincent AnnInst Pasteur 10 488 1896 13 609 1899) It is characterized usually by the development of painful, superficial ulcers, covered with an adherent, greenish gray membrane. Some fever is usually present and the submaxillary and





Fig. 1923 —Vincent's balanitis. (Madden J 105: 420 1935.)

Fig. 1924 —Fusiform bacilli and Vincent' spirochetes: smear from Vincent angina of which such microscopic findings are diagnostic. (Mead Diseases of the Mouth, Mosby)

cervical lymph nodes are swollen and painful. The mouth has a strongly fetid odor Salivation is copious. Swallowing and eating are painful, almost impossible The lesions spread rapidly The disease is usually acute in onset and its course is severe Fatality is unusual, but Henry (BMJ 1 1101 1936) reported deaths. Spontaneous healing may be expected after a few weeks but response to treatment is usually prompt. Superficial diphtheroid cases and ulcerative types are seen. Violent secondary infection may supplant mere shallow ulceration, so that noma supervenes.

Trench mouth is an infection and is transmissible. Vincent's organisms are present in almost all mouths, in the late dental crevices and the gingival trench. When circumstances are favorable, they multiply promptly Pellagra, scurvy and other nutritional disturbances predispose to and complicate Vincent's angina (Williams Tex SMJ 34 779 1939) The problem of the pathogenicity of oral organisms is still cloudy Vincent's disease may be virus infection the fusospirochetal organisms being only incidental (Fink JPediat 20 145 1942)

GENITAL FUSOSPIROCHETOSIS produces progressive and destructive ulceration of the external genitalia with copious purulent sanguineous discharge and not [illegible] (see Hamm: AmJTropM 18: 605 1938) Vincent's balanitis was manifested with [illegible] yellow ulcers, grayish preputial erosion, and phimosis in the case of Thomas (BMJ 1 485, 1943) See Gangrene, infectious Pellagra vaginitis in.

CHRONIC VINCENT'S INFECTION is believed to be comparatively common; certainly chronic ulcerative gingivitis occurs and in the lesions Vincent's organisms may be numerous. The bacteria in such cases are at least sometimes merely secondary invaders, and the underlying difficulty may range from stomatitis of malnutrition to that of contactant injury (see Stomatitis venenata)

SKIN INFECTIONS occur Some cases have followed bites or from striking fists against teeth. The lesion becomes an ulcer with putrid odor and greenish slough Erythematous patches, bullae and shallow ulcers were seen on the skin in 7 cases affecting the mouth severely wherein the outcome was fatal (Goldman and Cully: J 101: 358, 1933) Onychia and paronychia were reported by Benedek (Surg 11: 75, 1942) and purulent paronychia with ulceration beneath the toes was observed by Strickler (ADS 52: 87, 1945) The infection may complicate any chronic sore of the sacral region (Greenblatt and Wright: AmJSyph 20: 654, 1936)

VINCENT'S TREPONEMA is a delicate organism 5 to 10 μ long, having 3 to 8 irregular spirals. It stains poorly but uniformly is gram-negative and is actively motile. It can be cultivated under anaerobic conditions in serum agar and in serum broth growth occurring best at 37 C., not at all at room temperature Ellermann (ZntrblBakt 37: 729 1904; ZntrblHyg 56: 453 1907) found the organism in the depths of infected tissues, suggesting that it may be actively invasive. Tunnicliff (JInfectD 3: 145 1906) suggested that *T vincenti* and the fusiform bacillus represent 2 phases of the same organism but the balance of evidence is definitely against this view" (Topley and Wilson: Principles of Bacteriology Wood, 1937 p. 721)

Fusiform bacilli associated with filamentous forms have been found in various necrotic and ulcerative lesions in man and animals. They are pleomorphic, markedly so in some species. Some are motile; that associated with Vincent's disease is motile, according to Smith (Fusospirochetal Diseases, Wood, 1932) They can be cultured under anaerobic or microaerophilic conditions. In necrotic tissues, *B fusiformis* appears in long rods, 5 to 12 μ in length, thickened in the middle, possessing tapering or pointed ends. The bacilli are arranged singly or in pairs, end to end. They stain readily and are gram positive. Smith (1932) believed that fusiform bacilli may be dissociation forms of spirochetal forms.

Spirochetes found in the mouth include:

Spirillum sputigenum larger and shorter than *B fusiformis* comma-shaped, and actively motil

Spirillum nigrum (Rist) a small, thick, motile, curved organism, pathogenic for guinea pigs

Spirillum crassum: anaerobic, actively motile, fresh or in cultures

Treponema microdentium (Noguchi) 3 to 13 μ long, very delicate, tapering to pointed ends, having 4 to 6 coils when young and 12 to 16 in old forms; simulates *T pallidum*, except for the lashing activity with bending in the middle which the organism of syphilis manifests

Treponema mucosum (Noguchi) slightly longer and thicker than *T microdentium* distinguished from it with difficulty

Treponema macrodentium (Noguchi): fixed, rigid coils lik *T microdentium* but the coils are decidedly larger and coarser

Treponema buccale (Dobell) twice as wide as *T vincentii*, but like it in having irregular sinuous coils; its double contour due to its thickness distinguishes it on dark-field examination from other oral organisms.

Other organisms are found in the mouth including *B. gracilisformans* (Tunnicliff and Jackson) *Vibriothrix tonsillaris* (Tunnicliff) *Leptothrix buccalis* (Robin) *Bacterium m lanin-genicum* (Oliver and Wherry) and *Micrococcus gazogenes* *Bacteroides anaerobius* (Lenkowicz) These are of dubious parasitic ability

In any oral ulcer a variety of organisms is present. Mrzinowski (1922, quoted by Smith) produced fusospirochetal angina in a monkey by first scarifying a tonsil of the monkey then rubbing upon this lesion a bit of infected tissue from a human patient. Smith quoted other experimental inoculations of animals, but none is convincing

The bacillary form of *B fusiformis* may be the only one seen; in other cases the spirochetal one is associated. Other organisms also are commonly present. The tissue changes are those of extensive and rapid destruction of tissue without commensurate tissue reaction. A wide variety of lesions of the skin, ranging from eczema and pellagra to wounds, offer appropriate *locus minoris resistentiae* to receive the fusiform bacillus. The extraction of a tooth, or a tonsillectomy may be complicated with serious Vincent's infection.

The distinctively and consistently gangrenous feature of the lesions, the constancy of the presence of the bacillus, and the putrescent odor constitute reasons for believing the organisms pathogenic.

DIAGNOSIS.—Vincent's disease must be differentiated from diphtheria, suppurative tonsillitis, agranulocytic angina and syphilis. The pain, ulcers, membranes fetor acute course of the disease and adenitis are typical. The symptoms to which it gives rise are distressing and by continued extension of the involved area an attack may extend over a period of many weeks.

TREATMENT.—Arsphenamine intravenously has been recommended as a specific, but it is not. I have seen severe dermatitis following the use of arsenicals in this local condition which has been known to appear during anti

syphilitic treatment (Sutton J 83 1919 1924) When topically applied, the aqueous or glycerinated solution of neoarsphenamine is valuable (Rosebury et al. JInfectD 65 291, 1939)

Since penicillin became available other treatment has largely been set aside The intramuscular injection of large doses is extremely effective (Sweeney et al. JLabClinM 30 132, 1945 Joseph SouthMJ 38 778 1945 Pearce and McDonald J 128 342 1945) Penicillin lozenges (Page and Lipman NavMMonth 73 499 1946) or sprayings with 250 units per cc. (Strong and Willett USNMBull 46 353 1946) have also been highly recommended. Other antibiotics that are effective in syphilis should also cure Vincent's disease and are safer than penicillin Like syphilis, Vincent's disease has become in my experience a rare infection.

Locally hydrogen peroxide or sodium perborate as a damp paste is useful. The mouth must be kept clean by gentle measures, and dental hygiene and prophylactic treatment are indicated in the chronic cases. No immunity develops the disease becomes worse if untreated. Nicotinic and ascorbic acids and other vitamins may be needed. Fuadin intravenously for 6 to 1[?] injections was recommended by Smith (SouthMJ 35 290 1942)

Since sodium citrate kills spirochetes in vitro it may be worth trying in treating this disease (Leadingham JLabClinM 21 922 1936)

See Weaver and Tunnicliff (JInfectD 2 446, 1905) cultivation, Bloodgood (J [illegible] 1927) clinical description Vincent and Daufresne (ComptrendsocBiol 118 498, 1935), external review, culture of mouth spirochetes Farrell and McNichols (J 108 630, 1937) [illegible] cases occurring [illegible] deaths among 781 cases, involvement of larynx, trachea, lung, middle ear [illegible] hydrogen peroxide best [illegible] treatment of syphilis, neoarsphenamine not justified [illegible] treatment, Wintrup (Surg [illegible] 131, 1935) Rose (N Wliled 37 49 1938), treatment with tartar emetic Field (J 114 1072, 1940) zinc peroxide McKinney (HMJ 77 269 1940) H_2O_2 best, [illegible] and Greene ([illegible] treat underlying factors which allow saprophyte to flourish [illegible] of Negro school children [illegible] westM 24 20, 1940) incidence studies, found organisms in 41% of Negro school children King (Lancet 1 [illegible] Smith and Johnson (JPediat 17 1 1940), chromic acid treatment [illegible] 1940) nicotinic acid Lewis (ArchOtol 38 587 1943) bismuth by injection [illegible] (BMJ 2 380, 1943) development of disease in patients receiving [illegible] (Lancet 1 642, 1943) Mapharsen beneficial, Stahl (Lancet 1 640, 1943) [illegible] Linton (J 123 341, 1943) sulfathiazol locally, Craig (J 127 277 1945) [illegible] bismuth subsalicylate by injection; [illegible] tablets in mouth Grossman (BMJ 69 28, 1946) [illegible] (VaMMonth 74 31, 1947) (MilSurg 101 123 1947) control of epidemics Schuerman [illegible] relation to scurvy

Gonorrheal Stomatitis is seen in the newborn as an exceptional manifestation of birth canal infection much less common than gonorrheal ophthalmia. The tongue and palate show yellow white patches with acute inflammation, diagnosed by smears and cultures. The eyes should be protected with great care if they are by good fortune not coincidentally involved. Penicillin is promptly effective.

Streptococcic Gingivitis.—Streptococci may cause acute or chronic transient or persistent and moderate or violent disease of the oral mucous membrane or deeper tissues. They particularly favor the lymphoid tissue of the mouth for their habitat finding pyorrheic pockets, dead teeth and paradental abscesses also suitable foci. They may cause erysipelas, burrowing ulcer and scarlet fever as severe, acute infections. Less severe is a typical form of hypertrophic gingivitis due to *Streptococcus viridans*. Outstanding features are swelling pain and redness of the gums, palate and throat. The disease is acute in onset, and it is accompanied by fever salivation and malaise The soft gingival margins are bright red, rolled and edematous, the papillae being pushed up between the teeth. There is no ulceration erosion, vesiculation or membrane formation The disease generally responds within a week to treatment with local antiseptics and sulfonamide drugs (Woodburne JMichSM 34 284 1935)

Acute diffuse glossitis was fatal in 1 of 4 cases of McKinnon (JFlaMA 14 463 1928)

See Kelly (SouthMJ 4 286, 1931) gingivitis Woodburne and Northrop ([illegible] 422, 1934) McKinney (HMJ 77 269 1940) [illegible] stomatitis in children [illegible] herpetic.

Fissures of the Lip, multiple of shallow extent and of comparatively minor significance generally accompany contact and actinic cheilitis and respond to appropriate treatment of the underlying condition.

A solitary fissure chronic, painful and stubborn, is due to the streptococcus. The bottom of the crevice may contain inflammatory vascular tissue much like that of granuloma pyogenicum, excepting the gross configuration. In attempting to cure these the mobility of the lips interferes, and splinting such as would lead to cure of an analogous lesion of a finger is out of the question. One may drop hot cobblers wax on the sore or collodion, in order to immobilize while healing occurs (BMJ 1 370 1938) Michelson (ADS 10: 332, 1924) illustrated his method of performing a wedge-shaped excision of the whole lesion, stitching the edges so as to obtain primary healing and a straightline scar Sulfonamides by mouth and tetracycline ointment locally are promptly effective.

Lingual Tonsillitis.—The lingual lymphadenoid tissue ordinarily ana tomically inconspicuous, may become acutely more often chronically inflamed. The lymphoid tissues at the sides of the base of the tongue opposite the lower third molars, are the ones usually involved. Unilateral infection has been more common in my experience than bilateral, but occasionally the whole row of lymphatic nodules across the tongue in the region of the circumvallate papillae has been affected (Waldapfel ArchOtol 30: 269 1939) The com plaint is of persistent irritation, of variable degree, symptomatically most notable during mastication and swallowing Examination discloses a lesion consisting of a group of soft, reddened rounded papules, which may be fissured or excoriated, and from the crypts of which cheesy material may sometimes be expressed. A minute amount of bleeding may occur One must differentiate syphilis, tuberculosis and carcinoma.

Verruca and granuloma pyogenicum may spring from the lingual tonsil. Cancer practically never does.

The disorder has been carefully described by Sluder (AmJMedSci 156: 343, 1918), who noted follicular lingual tonsillitis as a recurrence f llowing faucial tonsillitis, and who believed the lingual tonsilla disease a significant focus of infection. Curtis (NYSJM 40 510 1884) thought that such trouble might infl ce singi g Several of my patient have been public speakers. Swain (ArchKlinM 39: 504 1886) described the anatomy of the region and reviewed 190 cases of hypertrophy of the skin glands" f the base of the tongue. Stöhr (Die Entwickl ng des Adenoiden Gewebes, Müller 1891) investig ted the embryology and histology of the lingual tonsillar tissue. Engman (ADS 1: 137, 1920) thought that this disease might be associated with burning tongue, causative perhaps in some cases. Rose (Lancet 2: 14 1927) recommended the actual ca tery in treatment of lingual tonsillitis Bothn (TransAmLaryngAssn 45 215 1923) listed the disorde as a cause of glossody ia; it is, rather a symptom of chronic streptococcic stomatitis, which may be symptomatically manifest as burning tongue or which may itself be dependent on vitaminosis.

Lingual tonsillitis may serve as a significant focus of infection believed Davis (Laryng 56 180 1946)

The most effective and promptly curative therapy is destruction, best performed by means of fulguration or the actual cautery using local anesthesia (Hollander J 102 1151, 1934) Infected teeth and those which scrape or traumatize the mucosa should be dealt with appropriately

Lingual Papillitis.—Solitary and isolated lingual papillae at times become the site of acute and evanescent simple inflammation (Scholtz ADS 32 801 1935) Those along the anterolateral aspect of the tongue in middle-aged persons with prostheses seem most liable to this disturbance. Momentary unipolar electrodesiccation without anesthesia is curative.

Peridental Infection.—Acute inflammation results from the action of virulent staphylococci, streptococci and other organisms, when they gain access to tissues about a tooth, beside it, beneath it, or within its pulp A dead tooth may be judged always to be infected. It may unexpectedly flare with vigorous inflammation, so that an acute cellulitis or abscess makes its appearance. Trauma, loosening the tooth, is a common incitation to infection. Caries may let in pathogenic bacteria. The type of infection and the individual s response to it determine the clinical course Staphylococci may be expected to produce acute purulent cellulitis which localizes, results in

abscess, and then may safely be incised and drained. Some staphylococci are dermonecrotic, so that the cellulitis is a sloughing one; compare Noma, which may appear as a complication of debilitating or exanthematous diseases and prove fatal. It is as dangerous as carbuncle of the face. Streptococci may provoke superficial gingivitis, erysipelas, purulent cellulitis, diffuse and burrowing cellulitis and sloughing lesions. Response to antibiotics or sulfonamides, if appropriate, is gratifying but abscesses have to be drained adequately

Pyorrhea Alveolaris.—The gingival trough deepens and eventually extends into the periodontal space, thereby forming slowly growing pockets, lined with epithelium. The trough collects débris of food, detritus of exfoliation and exudation, calculus, and the agents and products of fermentation. With discontinuity of the epithelial barrier inflammatory reaction may become either suppurative or granulomatous. The process extends toward the roots of the tooth so that the tooth is loosened, its sides bathed with pus or encased with granuloma. Three clinical types of involvement are described

Marginal Pyorrhea Alveolaris, with chronic purulent gingivitis and superficial pocket formation

Diffuse Pyorrhea Alveolaris, with deep pocket formation, suppuration and loosening of the teeth and

Precocious Senile Alveolar Atrophy which is often associated with deep pocket formation.

Acute pyogenic infection of a pyorrheic pocket may occur with the formation of an abscess and eventual discharge by perforation or by incision and drainage

Pyorrhea eventually heals itself the gums recede the teeth fall out, and the sockets heal with scar Pyorrhea is of importance as a focus of infection, for it harbors streptococci (Cokkinis BMJ 2 1168 1939) Its significance in internal medicine was stressed by Miller and Arvins (NYSJM 41 359 1941) who noted that in periodontia the area of absorption is considerably greater than in a mere root abscess Dermatoses frequently related with pyorrhea as a focus of infection are in my opinion, sycosis barbae lupus erythematosus, lichen planus pustular acrodermatitis, and chronic ulcer of the leg. Even syphilis, psoriasis and acne respond better to treatment when the mouth is medically clean. To cure pyorrhea Webb (Dental Survey Aug., 1935) advised destruction of gingival tissue external to the pockets, with fulguration, and providing adequate drainage. In severe pyorrhea, extraction is the only successful measure

Atrophic Gingivitis.—The gingival margins, including the slightly shrunken papillae are thickened and somewhat retracted from the teeth. "The normally arched gum festoons present an irregular broken line of angry-looking inflamed tissue The papillae may have a shriveled appearance or they may be partially absent and thus expose the approximal spaces between the teeth. The gingivae assume an engorged bluish red hue indicating passive hyperemia On raising the inflamed papillae hard dark masses of brownish or greenish calculus are observed which encircle the necks of the teeth. Upon pressure on the gum, pus may be seen oozing from the free margin. Occasionally the teeth may be slightly loose" The quotation is from Prinz and Greenbaum (Diseases of the Mouth Lea & Febiger 1939) Symptoms are not of discomfort but rather of foul breath and taste resulting from decomposition of débris and exudate The disease is one of neglected mouths of middle-aged persons. The description calls to mind the clinical picture of chronic paronychia The patient is benefited by practicing oral hygiene but trauma must be avoided. Avitaminosis must be taken into account.

These diseases may or may not be dermatologic ones but they are of dermatologic concern. The concept of the interrelationship of parasite with host is stressed, the basic facts being the same within the mouth as they are outside it. Dermatology and stomatology afford point-for-point analogies. While the mouth normally harbors a variegated flora, it is harmless, as the skin flora is harmless until a *locus minoris resistentiae* is offered, or until a new virulent pathogen is introduced into the equilibrium. Actinomycosis oft starts in a tooth socket. Other deep mycoses may start in the mouth, including sporotrichosis and cephalosporiosis.



Fig. 1925.—Cutaneous granulomatous abscess dependent on dental apical abscess, cured by removal of the tooth. (Mead: Diseases of the Mouth, Mosby.)



Fig. 1926.—Sinus tract through skin, originating from apical abscess of lower incisor tooth. (Anderson: J.A.D.A. 24: 1082, 1937.)

Focal Infection.—In chronic quiescent, peridental infection staphylococci or streptococci or both may be present and only inconspicuously active. Yet they are absorbed into the circulation in small numbers from time to time and like other foreign matter in the circulation tend to be filtered out at sites of inflammation. Thus, incidental benign cutaneous inflammation occurring in a person with a focus of infection (see p. 883) may become chronic dermatitis which manifests flares and recessions and which responds unsatisfactorily or not at all to local applications (Duke: Oral Sepsis, Mosby, 1918). There are

cases of chronic, recurrent pustular dermatitis, particularly of the hands and feet which can be cured only after foci of infection, especially oral foci, have been eradicated. Persistent bullous eruptions resembling staphylococcic impetigo were observed by Epstein (ADS 56 452, 1947) and could not be cured until dental foci were eliminated.

All dead teeth should be removed. Many persons live with them for years without apparent harm, but some people do not. In pustular acrodermatitis, pustular psoriasis, lichen planus, chronic urticaria, sycosis barbae recurrent herpes simplex about the face, chronic streptococcic stomatitis, including lingual tonsillitis, and chronic streptococcic dermatitis, dead, granulomatous, *abscessed or deeply pyorrheic teeth should be removed.* Pyorrhea (q v) ranks high as a source of focal infection (Christensen MJAustral 2 157 1941)

My conviction that dental foci of infection are medically important grows as my experience grows. Every dermatologist knows that asymptomatic tinea of a toenail may furnish reinfection which prevents lasting cure of dermatomycosis bacteria about diseased teeth provide a like service in many cutaneous lesions.





Fig 1927 —Abscess f palat due to periapical dental infection (Mead: Diseases of the Mouth, Mosby)
Fig 1928 —Lichen planus of buccal mucosa.

Sinus Tracts of Dental Origin.—Chronic inflammation about a tooth may lead to exudation and burrowing which may be practically asymptomatic like a cold abscess. Eventually the sinus tract ruptures through the gum, palate or skin. The influence of gravity leads to localization of the cutaneous terminus of the fistula in the chin as a rule It was on the chin that a lesion simulating granuloma pyogenicum developed in the case of Anderson (AJ[illegible] b 1062 1937) Hertzler (1938) depicted a similar example

Median mental sinus was the title under which 3 cases were described b[illegible] worth (BJD 5 57 1940) Carcinoma was sim lated by c ses of Montgomery (AD[illegible] 3 8 1940) The chin was the location of the gran l matous orifice of the sinus in the patie ts of Sh lton (ADS 4 939 1040) Lyell (BJD 61 [illegible] 1949) and J[illegible] Prest n (ADH 04 637 1051) The opening w s mandibular in that f Whittle (BJD [illegible] 464 1951) *The d sease may arise from* a buried root or from localized osteom[illegible] the mand bl (Gurdin and Pangman: PlasticRecon trSurg 11: 444 1953) The [illegible] may open through the gum t may open through the palatal mucosa or the cheek [illegible] of upper teeth The dermat logic importa ce f uch lesion lies [illegible] recognizing them

No local treatment can succeed of course until the abscessed t [illegible] extracted after which local treatment is likely to be unnecessary In a re[illegible] *view of the literature and presentation of 11 cases* Wende and Solomon (AJ[illegible] 46 665 194_ showed that removal of the infected tooth and curettage are curative.

Ludwig s Angina is an acute, spreading indurating cellulitis of the floor of the mouth and the neck. It is a well-defined clinical form of virulent bacterial parasitism, being due perhaps to both staphylococci and streptococci.

The original description stressed the comparatively slight inflammation of the throat, the woody hardness of the phlegmonous process, the involvement of the floor of the mouth within the border of the mandible, the well-defined border of hard edema in the neck and the absence of infection in the regional lymph nodes.

The disease starts usually from a carious tooth or following an extraction, spreading in the fascial planes of the submental and submaxillary triangles, causing serious illness by intoxication and by extending into the mediastinum perhaps or producing edema of the tongue and glottis so as to obstruct respiration.

Case records and extensive bibliographies were given by Grodinsky (Surg 5 678 1939) and Straus (Surg 6 230 1939), who found 38 cases in the literature, 2 of which proved fatal they gave the differential diagnosis from cancer tuberculosis, actinomycosis and gummatous syphilis. Sulfonamides were helpful in cases of Kayne (AmJOrthodont 28 98 1942) but did not always prevent progress to abscess formation which required surgical drainage. Streptococci were found in all of the cases of Williams and Guralnick (NEngJM 228 443 1943) who advised early radical surgery with exposure of the trachea in order to be able promptly to meet the exigency of respiratory embarrassment using sulfonamides and zinc peroxide they held their mortality to 10%

Penicillin, when it became available greatly reduced the need for surgical interference, reported Bean and MacKenzie (CanadMAJ 52 568 1945) It is common to prepare a patient for oral surgery with preliminary doses and coverage by antibiotics, and the incidence of the disease has diminished.

Thrush.—This is a manifest tion of moniliasis (p. 544)
Perlèche.—This is sometimes a manifestation of moniliasi (p. 544)
Deep Mycoses.—See Blastomycosis, Coccidioidomycosis, Actinomycosis, Histoplasmosis. A case f blastomycosis of the tongue a medical curiosity was reported by Sh lnjre (South MJ 21 169 1928) and the subject of primary blastomycotic infection of the tongue w s reviewed by New and Childrey (ArchOtol 12: 184 1930) Coccidioidal granuloma produces oral lesions, especially in cases with a gra e prognosis.

SYMPTOMATIC INVOLVEMENT OF THE MUCOSAE

Mucosal Lesions Incidental to Systemic Diseases, not of specific parasitic etiology are frequently seen. Few systemic diseases fail to manifest mucosal lesions at least occasionally The following conditions, described elsewhere in this volume, manifest mucosal symptoms more or less commonly

Amyloidosis
Angio eurotic edema
Avitaminosis deficiencies f ribofla in, niacin, folic acid ascorbic cid
Dermatitis medicamentosa
Dermatoses associated with gross malu tri tion oculo-oro-genital sy drome
Dysphagia and xerostomia in w men (Plummer-V son syndrome)
Endocrinopathies Add son disease Acanthosis nigricans; Acromegaly Myxedema; Pregnancy
Erythema m ltiforme mucocutaneous-ocular syndromes
Erythema symptomatica
Hemiatrophy
Impetigo herpetiformis
Lichen pla us
Liche scleros us; Balaniti rotica obliterans
Lipid proteinosis
Lupu rythematosus
Pellagra
Pemphigus ocull
Pemphigus vulgari and egetans
Psoriasis
Purpura, especially when ccompanied b agranulocytosis
Scleroderma
Skin and mucous membrane lipidosi
Urticaria

See Foerster (J 73 683, 1919) dermatoses associated with mucosal lesions Fox (Laryng 36 676, 1926), pemphigus in the mouth, Fox (PaMJ 38 408, 1935), oral lesions of systemic diseases; Mackle (J 104 176, 1935) in keratitis colitis one finds a flamboesa, inflamed lingual papill e, patha smooth trophy of tongue, diffuse stomatitis Boston (Military 84 473, 1939) pemphigus egetans i mouth; Bereston and Keil (ADS 44: 862, 1941) membranous stomatitis in uremia; Webb (SouthMJ 34 1130, 1941) bismuth stomatitis Dörner and Schuller (abs J 120 1346, 1942) dysentery associated with a lichenoids, herpes, gingi litis, stomatitis; Wood (ArchOtol 36: 666, 1942) oral manifestations of dermatoses Heimann (JIndustHyg 28 142, 1946) phosphorus.

Sarcoidal Cheilitis.—In "essential granulomatous cheilitis" of Miescher (Dermatologica 91 57 1945) the buccal tissues of the lips undergo sarcoidal enlargement and infiltration. The tongue and cheeks may be affected (Schuermann: Hautarzt 3: 538, 195..) Compare Melkersson's syndrome, wherein are associated relapsing facial palsy thick lips and lingua plicata, which also shows sarcoidal structure histologically (Richter and Johne: Affk.t 100: 487 1950) The disease may commence abruptly with swelling of the lips, or of the lower lip only thereafter persisting with incomplete regressions and relapses. Findlay (BJD 66: 129 1954) reported a case and distinguished the syndrome of Ascher (Klin MonatsblAugenheilk 65: 86 1920) which features swelling of the lips in association with relapsing edema of the eyelids and histologically only an increase of connective tissue and reticulofibrocystic changes in the glands of the lip. See also Erysipelas, recurrent, Melkerson's syndrome Elephantiasis, sporadic, and Cheilitis glandularis apostematosa.

Dermatitis Medicamentosa.—Drugs which often affect the mouth as a result of intoxication or allergy including those that may cause purpura and agranulocytosis (pp 755 1414) include the following (see p. 168 ff)

METALS	DRUGS	
Arsenicals	Acetanilid	Fluorides
Bismuth	Acetazolamide	Iodides
Chromate	Amidopyrine	Mesantoin
Gold	Aminopterin	Penicillin
Lead	Antabuse	Phenolphthalein
Mercury	Antihistamines	Quinacrine
Phosphorus	Antipyrine	Quinine
Radium	Apiol	Salicylates
Silver	Atropine	Sedormid
Thallium	Aureomycin	Streptomycin
Tin	BAL	Sulfocyanate
	Barbiturates	Sulfonamides
	Bromides	Terramycin
	Chloramphenicol	Thiouracil
	Cinchophen	Thorazine
	Dilantin	Tibione
	Ergot (ustilaginism)	Tridione

ARSENIC.—Local damage of considerable extent has resulted from improper use of arsenic for the purpose of destroying the pulp of a tooth. This practice is obsolete. Arsenical medication may cause purpuric or agranulocytic stomatitis.

BISMUTH.—Stomatitis complicating the use of bismuth in the treatment of syphilis can largely be prevented (1) by putting the mouth into a good hygienic state before starting heavy metals, a procedure in itself commendable in the treatment of syphilis, and (2) by avoiding overdosage recognizing sore mouth as a particularly sound reason for not giving more metal. The bismuth line will develop during the course of adequate therapy but stomatitis does not occur in a healthy mouth, ordinarily

CHROMATE.—In chromium plating, the worker is exposed, unless protected, to a spray containing chromic acid. Erosion and ulceration of the mucosae especially of the nasal septum will follow and the septum may be perforated. In the mouth, it i usually the region of the upper front teeth where damage becomes manifest. Inflammation swelling profuse serous discharge and the absence of pain characterize the process.

GOLD.—Used in treating arthritis and lupus erythematosus, gold may cause stomatitis simulating mercurial stomatitis, purpura or agranulocytosis.

LEAD.—Paint i the usual source of plumbism, for lead has no prominence as a medicament, except in an obsolete treatment of cancer Particles are absorbed via the digestive t resp ratory tract as a rule. Nausea headache, pallor diarrhea, and violent attacks of col c characterize subacute poisoning along with a sweetish lead breath and later wrist drop due to toxic neuritis. The lead li e on the gum margins is a fine stippled deposit of lead sulfide within the papillae and margi of the gums, densest about teeth covered with calcul possibly absent from a strictly clean and healthy mouth.

MERCURY.—Stomatitis due to mercury a it was once used in the treatment of syphilis wa as bad as the disease itself if not worse Necrosis of the jaw and sloughing of the teeth were commonpl ce As the use of the metal becam bett r understood later b cause evidences of such drastic poisoning with me cury became infrequent; later bismuth having pract cally supplanted it, mercurial stomatitis became rare. Salivation a d soreness of th teeth gi givitis with swelling and inflamm tion of the gums, loosening a d soreness of th teeth and secondary infection, are the oral charact ristics of intolera ce The pathogenesis of gingivitis i explained by the formation of irritating mercuric sulfide in that location if the concentration of mercury is high enough and if the h gienic condition of the mouth abets it A therapeut cally usef l concentration of mercury entail danger of stoma t and stomatiti once started rea lily becomes ulcerative because of fusospirochetal i

fection. The disease is easier to prevent than to cure. Sodium thiosulfate may be given intravenously. *In acute poisoning, Rosenthal (J 102: 1873, 1934)* recommended sodium formaldehyde-sulfoxylate in doses of 5 to 10 grams, given intravenously in 7% solution in water. The drug remains in the blood for several hours, is secreted by the kidneys, and is relatively harmless itself. It acts by reducing bivalent mercury to monovalent, compounds of which are insoluble. BAL is effective.

PHOSPHORUS.—Osteitis, periostitis, and necrosis of osseous tissue of the mandible, less often of the maxilla, result from phosphorus poisoning. Toothache, loosening of the teeth, inflammation of the alveolar processes, and suppuration, with discharge through the sockets of the teeth that fall out or through the skin of the chin, comprise the course of clinical events.

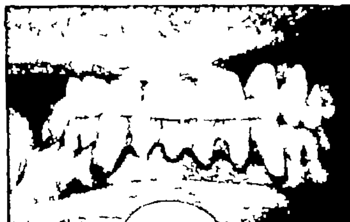


Fig. 1939.—Bismuth line from syphilotherapy. (Thoma: Oral Pathology, Mosby, 1954.)



Fig. 1940.—Hyperplastic gingivitis due to the use of Dilantin sodium. (Thoma: Oral Pathology, Mosby, 1954.)

Salivation and foul, garlic-scented breath are characteristic. Secondary infection following phosphorus-provoked necrosis of bone is the outstanding feature. Carious teeth are important localizing factors; it is said that phossy jaw does not occur when the teeth are sound (Prinz and Greenbaum). Once an occupational disease of match making, phosphorus poisoning should never be seen nowadays.

PLATINUM.—See Dermatitis venenata, metals (p. 146).

RADIUM.—Poisoning with radioactive substances, such as the painters of watch dials notoriously *suffered, results in* anemia through the effects of radioactivity on bone marrow, radium being metabolized much as calcium is. Necrosis of the jaw, secondary infection and the development of osteogenic sarcoma are typical features of this chronic, irremediable disaster (Evans: AmJPubH 23: 1017, 1933; AmJRoentg 37: 368, 1937). Diagnosis is

readily made with a Geiger counter. Decalcification increases the rate of excretion of radium (Evans: AnnIntM 11: 1443, 1938) so that parathyroid hormone or cortisone might conceivably be used to the patient's advantage.

SILVER.—Silver nitrate is a protein precipitant and caustic commonly used in the mouth and excellently effective. When used beyond the need, it coagulates good tissues along with the bad and produces ulceration. Absorption of silver salts leads eventually to argyria (q.v.), a slate-colored pigmentation affecting first the exposed part, in which the deposition of silver in the form of minute granules may be demonstrated in the tissues. In the mouth, a line of violet color, not blue, is deposited along the gum margin. This is inconsequential in itself, but it presages permanent discoloration of the exposed skin.

THALLIUM.—The acetate has been used to cause loosening of the hair in the treatment of tinea capitis (q.v.) by epilation. Its value for this purpose is considerable but great care must surround its use, for toxic doses are fatal. In thallium poisoning, as in poisoning with other metals, gingivitis and stomatitis are features, and the oral symptoms, with salivation and necrosis of soft tissues, are clinically important.

TIN.—"Tin picklers" are likely to suffer from marginal gingivitis (Prinz and Greenbaum 1939). Acid in the form of fumes, rather than metal poisoning, causes disintegration of the crowns of the teeth and intense inflammation of the gums. The blackened stumps of the teeth slough out.

Purpura.—Purpuric hemorrhage within the mouth may occur along with purpuric manifestations elsewhere, and the causes of oral lesions, which may be symptomatically conspicuous in thrombocytopenic purpura (q.v.), comprise all the causes of purpura in general. Oral lesions of purpura are bright red. Hemorrhagic blebs may form. Erosion and ulceration, with secondary infection of greater or lesser severity, are likely to accompany purpura. The gums may ooze blood. Investigations and treatment of purpura affecting the mouth are the same as in purpura in general.

Hemophilia, leukemia, hereditary telangiectasia, epilepsy, vicarious menstruation, pulmonary and esophageal diseases, and malingering must be considered in investigating bleeding from the mouth.

Agranulocytosis.—Angina is a major symptom of neutropenia, and agranulocytic angina is a recognized entity. Necrotizing inflammation of the tissues of the throat may accompany neutropenia of any cause; see Noma. While there may exist some cases of primary infection of the throat with symptomatic neutropenia, most cases of agranulocytic angina are necrosis consequent upon the loss of ability to withstand the attack of oral bacteria which are ordinarily harmless. Among the drugs which may cause neutropenia and thereby promote agranulocytic angina are

Acetanilid	Chloramphenicol
Acetophenetidin	Dinitrophenol
Aminopyrine	Neostibosan
Aminopterin	Nitrogen mustards
Antipyrin	Novaldin
Arsenicals	Phenylbutazone
Barbiturates	Quinine
Benzene, coal tar derivatives	Sedormid
Cinchophen	Sulfonamides

The destruction of leukocytes may be due to allergy, and thrombocytopenic purpura and agranulocytosis are closely related.

Agranulocytosis may be acute, even fulminating, manifesting angina of edematous, membranous or ulcerative type, with malaise, pyrexia, prostration, chills and inability to swallow. The posterior half of the mouth generally bears the brunt of the damage along with the pharynx, but the whole mouth, particularly the gingivae, may be involved. Such angina, along with a white blood cell count of perhaps only 1,000 cells per cu. mm., among which polymorphonuclear cells may be extremely sparse, characterize the disease from which it is possible death may promptly result. In chronic cases, symptoms other than leukopenia may be wanting except during exacerbations. Recurrent attacks of greater or lesser severity of symptoms may occur with the likelihood that a severe one may prove fatal (Mowbray et al.: QuartJM 1: 187, 1949).

Clinical and pathologic features found among the many cases of Norris (SouthMJ 28 504, 1935) included hypoplasia of the bone marrow profound neutropenia, secondary anemia, thrombocytopenia, jaundice, hemorrhages, lymphadenopathy splenic enlargement, ulcers of the mouth and elsewhere in the gastrointestinal tract, and thromboses of the small arteries. Complications included abscesses, septicemia, thrombophlebitis, pneumonitis with agranulocytosis, terminal hemorrhage and degenerative toxic changes in the brain, heart, liver adrenals and kidneys.



Fig. 1931.—Hemophilia spontaneous hemorrhages int the gums. (Thoma Oral Pathology Mosby 1954.)



Fig 1932.—Agranulocytosis spontaneous hemorrhages from gum margins. (Thoma Oral Pathology Mosby 1954)

Treatment with topical agents is comparatively valueless bland lavage being practically all that can be done Repeated transfusion is the most useful measure various chemical substances given by mouth or by injection being apt conceivably to increase the hematopoietic damage rather than to allay it Sulfonamides might have beneficial effects, but sulfanilamide has been known to cause the condition. Secondary infection is well controlled by means of antibiotics, as exemplified by the report of Boland et al (J 130 556 1946) who cured 11 cases with penicillin BAL might be appropriate in a case caused by metal intoxication if this were identified in the early stages when elimination of the metal from the system was feasible. Cortisone and ACTH have great value (Hart et al. BMJ 1: 1273 1952) their use has been discussed in the treatment of purpura (p. 759)

See Dermatitis medicamentosa and Purpura also Shelmire (SouthMJ 21 169 1928) several drugs causing stomatitis Greenbaum (DentalCosmos 6 252, 1924) medicinal oral lesions Gussman (DWchn 108 14 1939) severe buccal lesions from arsenicals Roerthl and Vogel (J 113 584, 1939) agranulocytosis from sulfapyridine Thompson and Gilroy (JAmDentA 28 1012 1941) Dilantin caused gingival hypertrophy curable only by plastic surgery Pine (ADS 43 426, 1941) fixed eruption limited to mouth from trisulfurea Dear (JAmDentA 30 651 1943) bismuth South et al (J 176 1027 1944) agranulocytic cases from Mapharsen, helped by penicillin Dameshek (Leukopenia and Agranulocytosis Oxford U Press, 1944, 74 pp) agranulocytosis usually due to drug, amidopyrine or sulfonamide, or allergic shock.

Noma.—Any gangrenous oral infection is called noma (Eckstein Am JDisChild 59 219 1940) A predisposing cause usually exists, such as devitalization of tissues from chemical injury chronic infection, deficient hygiene inadequate diet or avitaminosis. Agranulocytosis frequently the result of dermatitis medicamentosa (q v) is associated with ulcerative stomatitis, which is also a frequent concomitant of hematopoietic blastoma, especially monocytic leukemia (q v) Leishmaniasis accounted for most of the patients of Chu and Fan (ChinMJ 50 303 1936) more than half of whose Peiping cases of noma proved fatal. A few of them were associated with measles and



Fig 1933 —Noma in tertian malaria. (Marchionini, of Ankara, from Wiener Skin Manifestations of Internal Disorders, Mosby 1947)

Fig 1934 —Noma in malaria. (Marchionini, of Ankara, from Wiener Skin Manifestations of Internal Disorders Mosby 1947)

bacillary dysentery The disease increased in incidence during the period of enemy occupation and decreased when nutrition and hygiene improved after the departure of the Japanese reported Tupas and Jongco (PhilippMAJ 23 153 1946) Noma followed trauma in the case of Van Pavenswaay (JMoMA 35 17 1938)

In treatment, underlying causes must be attacked as effectively as may be Nutrition must receive attention. Medicinal agranulocytosis may respond to cortisone or ACTH Agranulocytosis from lymphoblastoma is hopeless but palliation may be attempted. Suitable antibiotic therapy is essential and reports following the introduction of penicillin into medical practice were justifiably enthusiastic (Herrell and Nichols AmJOrthodont 30 1 1944 Sung and Sung AmJOrthodont 33 254 1947) Cancrum oris in African natives previously standardly fatal was cured by Valzer (BMJ 2 14 1947) and by Mackay (BMJ 1 223 1949) Aureomycin was promptly effective in a case not responsive to penicillin (Fisher and Schwartz JID 13 1 1949) and it was dramatically beneficial in a patient with chronic ulcerative stomatitis when applied topically by Distelheim and Sulzberger (JID 13 115 1949)

The case of Tauber and Goldman (ADS 34 630 1936) seemed to be fusospirochetal, but proved fatal despite the use of arsphenamine. Surgical débridement is used as indicated. See also Gangrene of the face.

Perforating Ulcer in the mouth generally involves the palate and is generally due to syphilis. In syphilitic posterolateral sclerosis, teeth may spontaneously become loosened and their pulps become totally insensitive a sign pathognomonic of nervous system syphilis according to Prinz and Greenbaum. Perforating ulcer may occur in syringomyelia, leprosy peripheral vascular disease lethargic encephalitis, yaws, leishmaniasis, and poisoning with chromium and perhaps other heavy metals. Treatment depends on the cause. When the process is no longer progressive, prostheses or plastic surgery may be utilized to stop the gap which otherwise interferes with deglutition and phonation.

Metabolic Diseases.—The mouth is affected more or less considerably in the following diseases most of which are described in greater detail elsewhere in this volume

ACANTHOSIS NIGRICANS.—Pigmentation and papillation involve the mucosae.

ACNE VULGARIS.—A typical odor of the breath accompanies many cases.

ACROMEGALY —Bony distortion malposition of teeth and macroglossia are seen.

AMYLOIDOSIS.—In systemic amyloidosis glossitis is usually prominent

AVITAMINOSIS.—See pellagra, pernicious anemia, ariboflavinosis, perlèche Hunter's glossitis, glossitis of iron deficiency and scurvy

DIABETES MELLITUS or INSIPIDUS may cause xerostomia or avitaminotic stomatitis. Diabetic stomatitis is characterized by the deep red colo and extreme dryness of th mucosa. The tongue is likely to be swollen, showing indent tions of the teeth at its margins. Because of acidosis and the outpouring of phosphates, calcareous deposits about the teeth are particularly pronounced. Monilial secondary infection is especially likely because of the high concentration f sugar in all diabetic secretions. Rigid oral hygiene is essential. One should scale the teeth at frequent intervals, and one may prescribe mild alkaline mouthwashes. Met bolic balance must be obtained. Gingival pruritus may occur in diabetes (Stream: CanadMAJ 38 362, 1938)

HYDROA VACCINIFORME AND LIGHT SENSITIVITY —Vesicular or exfoliative cheilitis may occur; teeth may be red in porphyria.

HYPERPARATHYROIDISM results in cystic tumors of the jaw malocclusio nd distortion and hypermobility of the teeth (Strock NEngJM 224: 1019 1941)

HYPOGONADAL STATES in the climacteric or in castrates may be associated with dry burning mouth with leukoplakia and fragility of the mucosae, pallo and epidermal atrophy all esponsive to estrogenic therapy (Ri bman and Abarbanel: JClinEndocrin 3: 224 1943)

MENSTRUATION is sometimes accompa ied by oral changes. Vicarious menstruation, with bleeding from the gums and elsewh re instead of from the uterus, has been seen (Shelmire: SouthMJ 21: 169 1928) In menstrual relationship there may occur salivation, aphthae cyclic ulceration toothache herpes and rosion of the lips.

MYXEDEMA.—Thickening and enlargement f the tongue and lips are seen.

POLYCYTHEMIA causes burning and tenderness of the lips and mouth.

PREGNANCY —Marginal gingivitis, generally more marked about the lower front teeth is common. Rapidly advancing de tal caries may result from decalcification, a d may in part at least be controlled by the patie t's drinking milk and taki g calcium by mouth. Exace bation of soft tissue disease already present is to be expected.

Gingivitis of pregnancy begins about the second m nth of gestation a d lasts until the termination of it, and longer perhaps, even d ri g lact tion.

Fungoid growths of the gingival papillae are seen (Prinz and Gree baum) Epuli may develop and luxuriate during this time.

Hypertrophic gingivitis of pregnancy is a recognized clinical condition, swelling and diffuse hypertrophy becoming ma ked with the onset of mammary changes d ring the fourth month (Monash: ADS 24: 560, 1931; Schmitt: ADS 40: 653, 1939; Ziskin: JDentRes 18 367 1939) Edema, fibrosis, tenderness and a degree of fragility which makes bleeding easy are characteristic and may be xtreme. Monash (SGO 42 743, 1926) described 6 cases of inflammatory tumor de eloping during pregnancy th lesions being ot isolated but rather local e aggravation f the general gingivitis.

Pollutein injections cause the gums to dege rat an l become inflamed, and Progynon B promotes hyperkeratosis and hyperplasia of oral epithelium, so helping t keep the gums healthy reported Ziskin (JDentRes 18: 367 1939)

SCLERADEMA.—The tongue may be affected.

SCLERODERMA.—Oral involvement may be serious i generalized cases in which the head is invol ed, interf ring with deglutition. Oral involvement i usually a late symptom.

UREMIA has been reported to cause membranous stomatitis (Bereston and Keil: ADS 44 562, 1941) The mouth may manifest the symptoms of xerostomia due to high osmotic

pressure of tissue fluids and to the withholding of water from a patient incapable of taking it. In coma, the diminution of salivary flow and the failure of the patient to keep the mouth clean lead to luxuriation of the oral flora and to incrustation of the oral tissues with gluey exudate and pultaceous pseudomembranous matter. *After removal of such a coating the mucosa is red, tender and possibly ulcerated.* Careful nursing should succeed in preventing this. If rather than mere muck and fermentation, pathogenic organisms are the cause of ulceration sloughing even of the teeth may ensue.

XANTHOMA.—Xanthomatous infiltration of the gums may be marked in Gaucher's disease (Cohen and Fisk: J Lancet 59 19[illegible] 1939). Bleeding from the gums may be severe in terminal stages. In diffuse xanthomatosis of skin and *mucosae* oral lesions are pronounced. *In pseudoxanthoma elasticum* oral lesion may rarely occur.



FIG. 1935.—Gingivitis of pregnancy. (Thoma: Oral Pathology, Mosby 1931.)



FIGS. 1936 and 1937.—Gingivitis of pregnancy. (Drs. Maier and Orban, from Thoma: Oral Pathology, Mosby 1931.)

Avitaminosis, Iron Deficiency and Stomatitis (Hunter's Glossitis).—In severe anemias and sprue the tongue is sometimes so atrophic that it weighs only 60% of the normal amount, and this is due to diminution in the quantity of muscular tissue as well as to superficial atrophy (Hunter: Severe Anemias, Macmillan 1909). Anemia is clinically obscured in many cases by the [illegible] of inflammation. The mucosa and submucosa may harbor *Streptococci* [illegible] dens in these cases (Schneider and Carey: Minn M 10 [illegible] 14 1927).

In pernicious anemia, atrophy of the papillae of the tongue is typical affecting the sides, particularly and the redness of the inflamed lingual mucosa stands in contrast to the pallor of the remainder of the mouth Burning and stinging sensations at the borders and tip of the tongue are concomitant complaints. Stomatitis of pernicious anemia is symptomatically benefited by successful antianemic treatment, which must include an ample supply of B complex especially vitamin B_{12} and folic acid (q v)

Anemia of the sort benefited by large doses of iron is associated also with glossitis (Dameshek: J 100 540 1933 Darby: J 130: 830 1946) Alcoholism causes glossitis which is identical with that of pellagra (q v) and proper diet and nicotinic acid are promptly effective (Blankenhorn and Spies J 107 641 1936) Stomatitis in avitaminotic states was discussed by Topping and Fraser (PHRpts 54 416 1939) and Manson Bahr (Lancet 2 317 356 1940) Lack of pyridoxine caused sore tongue in the case of Rosenblum and Jolliffe (J 117 2245 1941)





Fig. 1938 —Smooth tongue of primary anemia.

Fig 1939 —Scurvy showing gingival swelling and petechiae. (Mead: Diseases of the Mouth, Mosby)

See A Hashimoto; Pellagra, Starvation; Dysphagia and xerostomia. Burning tongue, also Middleton (Anni thl 6 352, 1932) imprints of tongue on smoked paper show papillation changes in anemia, pellagra, sprue Middleton et al (J 101 1398, 1933) avitaminosis B and atrophy of lingual papillae t Wilhelmy (JKansMS 35 430, 1934) Hunterian glossitis, achylia and anemia; Bethell et al. (J 103 797 1934) third f patients with iron-deficiency anemia had recurrent glossitis followed by trophy Margolis and Smith (JNutrit 10: 841 1938) nicotinic acid cures blacktongue in dogs; Manson-Bahr and Ransford (Lancet 2 426, 1938) nicotinic acid cures sore tongue of pellagra Aykroyd et al (Lancet 2 825, 1939) stomatitis in Indian tea workers often responsive t nicotinic acid K [illegible] (Lancet 1 1260, 1939) "winter glossitis" in Palestine often respond t nicotinic acid although other signs of pellagra absent; Griebel (KlinWchn 19 496 1940) lingual tuberculosis and related avitaminosis; Wien and Sleeman (ADS 41: 1160 1940) crusted cheilitis case cured with B complex; Jeghers (NEnglJM 227 221 1942), tongue in nutritional deficiency Machella (PaMJ 45 941, 1942) oral manifestations of deficiency of water-soluble vitamins; Fraser and Topping (PHRpts 57 968, 1942) experimental avitaminosis C in monkeys; Kaufman and Smith (J 121 168, 1943) glossitis with papillary atrophy constant feature of sprue, nonspecific histology; Langille (CanadMAJ 50: 141, 1944) stomatitis and conjunctivitis case cured with vitamins B and C Cayer et al. (SouthMJ 38: 111, 1945) cheilosis not usually vitaminotic but may be; laboratory diagnosis of nutritional status; Beveridge and Kyhos (AIntM 76 31, 1945) lingual fissures and atrophy helped with nicotinamide; Laughorne et L (CanadMAJ 54 166, 1946) requirement of vitamin C to relieve gingival deficiency exceeds 25 mg per day approximates 75 mg.; Keele and Bound (BMJ 1 77 1946) glossitis in sprue almost invariably with soreness t tip of tongue, spreading to sides, variable in intensity, perhaps paralleling diarrhea, cheilitis in less than half the cases; Smith (BMJ 2 488, 1946) asymptomatic glossitis in British troops in India, with patchy baldness, erythema and fissuring only partially relieved with vitamin B; Brown (BMJ 1 704, 1949) in pernicious anemia, 7 cases 1 responded t nicotinic acid or folic acid, 4 to calcium pantothenate; Schieve and Rundles (JLabClinM 34 439, 1949) glossitis of pernicious anemia only sometimes or partially relieved by folic acid, als [illegible] by [illegible] Schoenbach et al (J 144 1558, 1950) citrovorum factor prevented stomatitis from folic acid deficiency induced by Aminopterin Sinclair (Practit 166 133 195) oral manifestations of deficiency diseases, review; Rastrup-Madsen (abs J 151 623, 1953) chronic glossitis without anemia in 3 patients with latent pernicious anemia and achylia, cured quickly with liver injections or B_{12}

Nonblastomatous Leukoplakia.—Any lesion in which there is proliferative superabundance of epithelium causes leukoplakia when it occurs in the

mouth. By contrast, when epithelium is thinner than normal, the color is redder and the majority of inflammatory oral lesions produce erythematous rather than leukoplakic lesions. Inflammatory leukoplakia is often seen in mucosal lichen planus, sometimes in stomatitis venenata. It occurs when the individual chews his cheeks. The monilial lesions of thrush are white and the membrane of diphtheria can be considered leukoplakic for purposes of discussion. When the mucosae are swollen and the teeth make indentations on the buccal tissues, epithelium may be thick and whitish between the depressions. The causes of vulvar leukoplakia are various (Ellis and Ketron SGO 61 635 1935) see kraurosis (p. 1031)

Plainly there is no one method of treatment applicable to all kinds of leukoplakia. An effort must be made to discover the cause. Since the leukoplakia of inflammation is different in significance and treatment from neoplastic leukoplakia (q v) the distinction is important. Much leukoplakia of the inflammatory type may safely be neglected, as coated tongue may be as a rule. Often the cure rests on keeping something out of the mouth, mouthwashes included. Tobacco walnuts, pecans and chocolate are common causes.

Syphilitic leukoplakia is distinguished by its thick, white patches, which are circumscribed, oval, usually crowded together in a mosaic, located on the dorsum of the tongue, and set on syphilitic glossitis it is likely to be neoplastic in reality

Catarrhal Stomatitis is the title applied to simple stomatitis superficial in character with redness, swelling mild desquamation and either dryness or serous exudation. It may be eczematous or bacterial. It is synonymous with mild stomatitis of undetermined cause.'

Marginal Gingivitis is acute or chronic inflammation of the gum margins affecting the papillae and the labial and lingual aspects of the gums. Causes include everything that may injure the gums, ranging from calculus through chemical irritants and scurvy to leukemia. Marginal gingivitis is diagnostically as definitive as sore leg

When the gums are sore the teeth should be cleaned gently with a soft brush and a nonirritating dentifrice The mouth should be kept clean, and débris should be removed. Barring the possibilities of medicinal irritation, nutritional and hormonal inadequacy and neoplasia these measures should result in improvement. Applications of possibly irritating medicines are to be avoided. I have seen silver nitrate chromic acid and iron chloride peel off the epithelium and prevent its replacement. Physiologic salt solution is safe economical and never allergenic. In the practice of dermatology one ever wonders at the frequency with which doing nothing intelligently is the best thing Healing results from keeping things off rather than from putting them on masterly inaction was Stokes phrase.

Xerostomia, or dry mouth, occurs when the salivary glands are atrophic as a result of congenital aplasia of the salivary glands, avitaminosis or the influence of roentgen rays. It occurs *when the individual* ingests little fluid, perhaps because of sore mouth, esophageal constriction or sore urethra Fever dehydration, diuresis, diabetes mellitus, diabetes insipidus, opiates atropine, senility and psychiatric disorders are among the possible causes (Tilley Lancet 1 183 1931) Sialoliths, obstructing the salivary flow and actual absence of major salivary glands because of their surgical removal may produce the symptom. The dried mucosa is especially susceptible to fissures, bacterial infection and mycotic parasitism. It must be kept moistened by petrolatum and frequent lavages with physiologic salt solution. The vitamin B complex may be needed and the diet must be adequate (Chamberlin J 95 470 1930) Liquid petrolatum may be sprayed into the mouth and gives some satisfaction at times. The underlying situation must be controlled if possible Usually the patient must obtain more fluid, perhaps by the intravenous route.

See Dysphagia and xerostomia in women; also Hutchinson (TransClinSocLond 21: 180, 1888) early description of xerostomia; Greenbaum and Tumen (J 107 1297 1936), from x-ray therapy of hirsutism; Saphir (AmJDigestDis 7 298, 1940), cases cured with nicotinic acid; Faber (ActaMedScand 113 69, 1943) etiology; QBIN (J 134; 466, 1947) investigation of case; Allington (ADS 62: 829 1950) etiology frequently accompanies rheumatoid arthritis with keratoconjunctivitis sicca and high sedimentation rate.

Ptyalism.—Excessive salivation occurs in bulbar paralysis mercurial intoxication, morning sickness of pregnancy painful lesions of the mouth, and psychosomatic disorders It is a feature of nausea, whatever the cause may be Dribbling from the mouth is normal in infants and during sleep It occurs in dementia and idiocy when the mouth is left open, and in some schizophrenics who refuse to swallow It is seen in macroglossia or facial paralysis as a result of inability to swallow See Thoma (Oral Pathology Mosby 1941 p 1141)

Fetor Oris, conveniently named halitosis, or disagreeable odor of the breath, is almost always due to local causes (Sanarelli: PresseM 46 1449 1938) I think that it has been proved that odorous substances can circulate through the blood and so reach the lungs, so as to be exhaled in recognizable concentration (Crohn and Drosd J 117 2242 1941) a proposition debated by Goodman and Berg (J 108 136 1937) If this is true of the respiratory epithelium, it may be true of the sudoral epithelium see Bromhidrosis.

Halitosis has many possible causes. Usually they can be found; often they can be corrected. Detection of the cause requires adequate examination of the patient. Foci in the upper and lower parts of the respiratory tract may not be obvious and may include bronchial infection, sinus infection, chronic nasal catarrh, atrophic rhinitis, adenoids and chronically diseased tonsils. The intestinal tract may be a source, with causes ranging from esophageal diverticulum, gastritis, cholecystitis and colitis to faulty fat metabolism. Gastrointestinal allergy is said to be a cause Smoking may contribute to both odor and oral irritation.

Objectionable odors arise usually from stagnation and fermentation of food débris in the mouth. Bad hygiene calculus, pyorrhea and decay abet this. The odor of fermenting blood serum may result from too strenuous efforts to keep the mouth clean. Tonsillar crypts may contain odorific caseous material, and nasopharyngeal troubles may be the source. Metabolic disturbances such as scurvy purpura, uremia, diabetes, cirrhosis of the liver acne, hunger fatigue menstruation and intoxications of various sorts modify the smell of the breath

Cases require and merit careful consideration. They are usually responsive to suitable treatment, unless the patient, having read the ads, is only imagining things. The worst complainers are those who do not have the disease while many who suffer from it are not aware that they do (Drosd and Crohn AmJDigDis 9 79 1942); compare Bromhidrosiphobia. See Squamous carcinoma treatment, palliation (p 1235)

See Bromhidrosis; also QBIN (J 111 1966, 1938 113 2170, 1939) buccal carcinoma and fetor oris; Thoma (Oral Pathology Mosby 1941 p. 1142) Castellani and De Silva (TropMedHyg 55; 51 1952) *Escherichia coli foetida* has remained stinking for 31 years Becker (MünchMedWschr 94 2226, 1952) chlorophyll as deodorant reduced nasal fetor

Neural Lesions of the Mouth.—Peripheral lesions of the ninth nerve cause loss of taste on that side in the anterior two-thirds of the tongue Integrity of the facial nerve, vulnerable in various ways, is important for normalcy of the mucosa of the lips and cheek on that side and also of the conjunctiva. Bulbar palsy neurosyphilis, poliomyelitis and syringomyelia may cause atrophy of the tongue by damaging the twelfth nerve which supplies lingual motor innervation. Buccal neuralgia may require division of the facial artery vein and sympathetic nerves (Reichert: ASurg 41 473, 1940) or injection of the mandibular branch of the trigeminal nerve See Costen s syndrome (p 1433)

Glossalgia.—Tic douloureux may involve the ninth cranial nerve affecting the oral mucosa and tongue (Hoover and Poppen J 107 1015 1936) Herpes zoster (q v) may appear within the mouth. Unilateral tingling and paroxysmal pain in the mouth were cured in several cases of mine by intracutaneous smallpox vaccination (see Segmental neuralgia)

Psychotic Disorders.—Sucking the tongue, chewing the mucosa of the cheeks or lips, compulsion neuroses involving weird manipulations of the organs of the mouth, and oral erotism deserve mention. Cancerophobia, often grounded upon the patient's discovery and misinterpretation of lingual tonsillar tissue or circumvallate papillae is a disorder the stomatologist may treat. See also Psychosomatic aspects of dermatoses, and Dermatitis artefacta.

Dysgeusia (Taste Abnormalities)—*The sense of taste is to a considerable* degree dependent upon that of smell organic disorders of which may appertain, ranging from a cold in the head to a tumor of the brain. Wearing a new upper denture made of material tasteless in itself may be followed by marked loss in the sense of taste and therefore by anorexia even of consequential proportions (Pusey J 114 1548 1940) Impairment of taste following tonsillectomy was noted by Dehnen (ZtschrLaryng 29 546 1950) Methylthiouracil, given in treatment of thyrotoxicosis, has caused loss of the sense of taste during the period of its administration, with recovery after its discontinuance (Schneeberg J 149 1091 1952 Hallman and Hurst J 152 322, 1953)





Fig. 1040.—Lip sucker's cheilitis. (Dr Sam Sweitser)
Fig 1041—Lip sucker' cheilitis, with resultant d pigmentation (Dr O G Costa)

Aberrations of taste may result from secretions or secretions about the teeth, decay or pyorrhea giving rise to putrid effects seldom of themselves sufficiently cogent to induce a patient to seek the oral surgeon he should. A fistula between the antrum and the mouth produces a persistent salty taste (Robinson J 147 100 1951) Taking various drugs will cause a persistent bad taste notably digitalis, iodides, mercury and gold.

Oral herpes zoster (q v) can cause dysgeusia It may be experienced as an aura of migraine or epilepsy Both loss of taste and bad taste occur as occasional manifestations of hysteria, schizophrenia and dementia, although they may represent merely an anxiety state and respond to reassurance and phenobarbital.

PIGMENTATION

Normal Pigmentation of the mucous membrane is comparable with that of the skin melanophores and dopa positive cells being numerous in the oral mucosa (Becker ADS 16 259 1927) *Pigment may be melanin, hemosiderin*

or other substances, such as deposits of metals, for tattoo of the mouth occurs. Depigmentation as well as hyperpigmentation may take place. The color of the blood affects the color one sees.

Abnormal Pigmentation.—A list must here suffice of disturbances of pigmentation as seen in the mouth (see Castor JTropM 15 117 1912 Monash: ADS 26 139 1932)

Acanthosis nigricans (q v) and Addison's disease (q.v) cause oral melanosis.
Anemia: Pallor of the mucosae may be notable
Arsenical pigmentation (q.v) may affect the mouth as well as the skin.
Avitaminosis: pellagra (q.v) may be accompanied by mucosal hyperpigmentation
"Blue gum," normal spotty pigmentation occurring in Negroes.
Carbon monoxide poisoning: mucosae appear brighter red than normal.
Cyanosis.
Intestinal polyposis (p. 792)
Jaundice.
Leukoplakia (q v) alters the color of the site.
Melanoma (q.v) may occur in the mouth.
Melanoplakia is the name applied to pigmentary spots possibly existing normally sometimes appearing with leukoplakia superimposed on them.
Metal deposits including bismuth lead, silver mercury
Methemoglobinemia, caused by various drugs the mucosae become blue.
Normal pigmentation is variable and may be spotty
Phthiriasis, causing general cutaneous pigmentation and cachexia, may also cause oral pigmentation (Thibierge: AnndeD 1892, p. 734)
Polycythemia results in purplish redness of the mucosae.
Quinacrine occasionally causes slate blue spots.
Tattoo (q v) of the tongue or gums with ink or charcoal.

Mucosal pigmentation has been described as symptomatic of ancylostomiasis. Leonard (J 45: 588 1905) wrote

"In every case of ancylostomiasis under my treatment with the exception of poor whites of European parentage the pigmentation of the tongue is seen. It consists of minute black, blue-black or brown spots, usually on the tip and sides of the tongue; sometimes the pigmentation is seen in larger areas. The colored races in this island [Grenada, British West Indies] viz., the Negro East Indian and their descendants show they pigmentation in every case of uncinariasis, and it is especially marked in the chronic cases. In these the pigment is deposited chiefly in the mucosa of the papilla in its lower layers. This pigmentation of the tongue and buccal mucous membrane and mucous membrane of the intestine has some connection with the disease and may be taken as of diagnostic value, for I have never failed to find the ova and other symptoms of the disease present in any case which showed this pigmentation. Pigmented spots were noted in the intestines along with hemorrhagic spots in 4 cases in which Leonard performed necropsies.

According to Castellani and Chalmers (Tropical Medicine, Wood, 1919 p. 1765, p. 2265) "Some observers say the tongue shows 2 purplish smears one on each side and is pigmented; but this in our experience can be seen in normal natives. In some races the oral mucosa is not pigmented, in others there is dark pigmentation which extends often out the tongue. Dark patches on the tongue have been considered to be a pathologic condition and a sign of ancylostomiasis. We have observed such patches, however in numbers of normal natives."

The occurrence of pigmented macules on lips, cheeks, tongue and palate has been remarked by many authors. When congenital or appearing in early life, they might be of the same nature as brown or blue nevi and Mongolian spots. In colored races, pigmented macules may represent mere irregularity of melanin pigmentation, more apparent on the less deeply pigmented mucosa than on the skin.

Pigmentation of the lips was described as follows by Pusey (ADS 36 613 1937):

For many years I have observed pigmented spots on the inner surface of the lips which have appeared spontaneously and without symptoms. The condition is evidently rare. The lesions consist simply of small pigmented spots without elevation, infiltration, or changes in the surface of the skin. They are dark brown almost black, and irregular roughly circular and measure from or 3 to 8 or 10 millimeters in diameter. They are not associated with abnormal sensation and usually cause the patient to seek advice because of curiosity or fear. In most cases they are limited to the inner surfaces of the lips, more often on the lower lip. In some cases there have been lesions on the buccal mucosa. They have not been associated with anomalies of the skin or disturbances of the general health.

I have not examined any of them histologically, but I have no doubt that a biopsy would show simply normal pigment in the usual location. The lesions have not been suggestive of malignant diseases. They are I believe, dyschromia without significance a clinical curiosity I have made no effort to remove the lesions.

In a case of such lesions of the lip examined histologically by Col. W F Harvey and me sections showed only melanin pigment in dendritic cells, some of which were densely packed with granules these were situated in the tunica propria, while the basal cells of the surface epithelium were also laden with melanin. The margin of the anomaly was as sharp in sections as in the gross.

Discolorations of the Teeth.—Green teeth have been seen in the first dentition of children who were severely jaundiced in infancy This curious vestige was observed in children born to Rh negative mothers with Rh-positive mates. The color due to altered blood pigment deposited in the tooth buds, of the central incisors especially ranged from green to brown, according to Hackett (IrishJMedSci 319 324, 1952)

Yellow teeth have been seen in cadmium workers. A yellow fringe forms at the dental collum most pronounced on the incisors and front teeth sometimes involving the molars, in individuals who have worked with the metal for many years (Baader J 152 514, 1953) The discoloration has been noted on a false tooth. It is pathognomonic of chronic cadmium poisoning.

Red teeth are sometimes seen in congenital porphyria (p. 718)

Figs 1943 and 1942.—Pigmentation of the lip, showing lesions of mucosa, dendritic cells in the basal epidermal layer and melanophores glutted with pigment granules in the dermis. (Col. W F Harvey)

See Dermatitis medicamentosa, bismuth, phenolphthalein, quinacrine, all et M [illegible] Acanthosis nigricans, Tattoo also Oddo (AnndeD 1906, p. 303) patchy, as in dogs [illegible] review [illegible] field (BJD 19 202, 1907), acquired melanoplakia, case A thony (J 61 1665, 1913), [illegible] physiologic pigmentation of [illegible] Lortat Jacob (BullSocMedHopParis 33 [illegible], 1912), physiologic [illegible] brunette; Chabert and Mc [illegible] Pichler (WienMWchn 63 608, 1910) melanoplakia in normal [illegible] Lortat Jacob [illegible] Donald (JTropM 24: 72, 1921), pigmented spots on tongue in [illegible] Reiche (MedKlin 20 [illegible] pigmented spots Solente (BsocfrancD 30 363, 1923), melanoplakia, case; [illegible] peptic ulcer, but pigmented [illegible] melanoplakia related frequently t hepatic cirrhosis and [illegible] (JAMA 40 [illegible] occur in half of individual of colored races; Arnozan and [illegible] (ADS 131 601, 1936) illustrations [illegible] melanoplakia, 3 cases; Fordyce and Machee (ADS 13 [illegible] 1926) bismuthia Löbe and Rosenfeld (MedKlin 23 1796, 1937) [illegible] (ADS 17 749 1928) physiologic canine type, case [illegible] and [illegible] 1937), Addisonian case attributed to syphilis of [illegible] Milian and [illegible] 34 401 1937) melanoplakia attributed t syphilis Pichler (abs [illegible] melanoplakia attributed t tobacco-chewing; Milian and Lamay (BsocfrancD [illegible] 1931) argyria [illegible] melanoderma phthiria ique with melanoplakia, [illegible] (ADS [illegible] 1931) anomalous oral pigmentation [illegible] silver arsphenamine Kistiakovsky (ADS 24: 247, 1931) [illegible] including pigmentation [illegible] Merrifield (JAmDentA 0 27 1933) gingival diseases [illegible] from lip [illegible] RoySocM 30 530, 1937) progressive macular lesion spreading [illegible] 1939) melanoplakia, case [illegible] syphilitic [illegible] 10 cases, dominant [illegible] 1031, 1949), oral melanotic spots [illegible] intestinal polyposis, 10 cases, [illegible] heritance; Dell et al. (ADS 66 [illegible] 1952) tattoo from [illegible] localized argyria.

DISEASES OF UNKNOWN CAUSE PECULIAR TO THE MOUTH AND MUCOUS MEMBRANES

Epulis, a name as inexplicit as eczema, is any growth involving the gums (Anderson Arch Surg 38 1030 1939)

GIANT-CELL EPULIS is a well-defined type of benign tumors which recur if the removal is incomplete. They are of pea to hickory nut-size as a rule, but may be considerably larger especially in the upper jaw They form rounded





Fig 1944—Peripheral benign giant-cell tumor of the maxilla. (Thoma: Oral Pathology Mosby 1944)

Fig 1945—Peripheral benign giant-cell tumor of the mandible. (Thoma: Oral Pathology Mosby 1944.)



Fig. 1946—Giant-cell tumor shown in Fig. 1944 (Thoma Oral Pathology Mosby 1944.)

tumors between or about one or several teeth. They generally arise about a single tooth, and may spread and extend so as to involve adjacent teeth. The color is generally that of the surrounding mucosa, which is undergrown by the tumor Giant cells are remarkably prominent in the histologic structure and the more malignant one is, the fewer the giant cells (Hertzler) To cure these their bases being attached to the root of one or more teeth, it is neces-

sary to sacrifice the tooth or teeth along with the border of the alveolar process and sometimes considerably more. *Rarely they are malignant* (Sachs and Garbe ADS 38 603 1938)

FIBROUS EPULIS applies to miscellaneous local hypertrophies of the mucosa due to nevus, neurilemmoma, *fibroma* or fibrosis.

ANGIOMATOUS EPULIS is a *soft*, red lesion, a granuloma pyogenicum.

ANGIOFIBROMATOUS EPULIS, a painless, benign tumor covered with epithelium is probably a synonym of local hypertrophy

Local Hypertrophy of the Gingival Tissues or of the mucosa of the inner surface of the lip may *form locally* in response to suction or distortion by dentures Ridges of fibrous tissue may develop on the alveoli so as to form folds of excessive but not inflamed mucosa, tumor formation being the result of mechanical agencies (*Kazanjian* NEngJM 201 1200 1929)



Fig 1947—Fibrous epulis local hypertrophy of buccal mucosa, probably due to ill fitted denture. (Dr Erwin Zeisler)





Fig. 1948.—Granuloma fissuratum typical fissured lesion in lower labial ... (Sutton ADS 26 ... 1932.)

Fig. 1949.—Granuloma fissuratum sectioned across the fissure showing inflammatory ... the fissure structure and intense polymorphonuclear leukocytic inflammation

EPULIS GRANULOMATOSA is a name for a benign, noninflammatory mucosal tag when it occurs on the buccal mucosa, located often opposite a missing molar (A... and Anderson ADS 36 1140 1937) The lesion is a whitish or pinkish, firm, asymptomatic mass covered with epithelium composed of vascular areolar tissue resting on an ... shaped base which is not indurated. The surface may be lobulated or smooth ... It is like an uninflamed hemorrhoidal tag The lesion may be pedunculated or sessile ... benign. Its existence depends mainly on mechanical factors. It is distinct from ... inflammatory hypertrophy of the gums, and from the malformation ... normal ... Histologic examination shows normal epidermis supported upon loose, ... but excessive areolar tissue Since the fleshy tumors are in the way they require removal ... This can be done simply by infiltrating the base with a local anesthetic and ... the disc of mucosa at the line of attachment with the actual cautery The wound ... and heal in a week or two with trivial scarring

Granuloma Fissuratum is a peculiar circumscribed, firm, whitish fissured, granulomatous and fibrotic epulis occurring in the labioalveolar fold. The lesions are discoid, smooth rounded and slightly raised. They are about a centimeter in diameter lack an inflammatory areola and are folded like a bent coin so that the fissure in the bend is continuous at both sides with the labio-alveolar sulcus. I have seen a case without a fissure in the fold. Symptoms are slight. These benign nodules represent inflammatory reaction in buccal tissue to mechanical agencies, being perhaps both traumatic and bacterial in origin perhaps representative of streptococcic fissuring mechanically delayed in healing (Sutton ADS 26 425 1932) In diagnosis, carcinoma must be excluded Excision is curative I have yet to see conservative methods prevail.

The lesions were located in the superior sulcus in my origi al cases and in the inferior sulcus in 1 of Sutton, Sr (ADS 26: 865 1933) The case of Diasio (ADS 25: 5°1, 1933) involved the lower f ld, but th fissure was abortive Appel (ADS 28: 751 1933) assumed the upper plate the etiologic factor Mead (1933) depicted n example asserting that the hypertrophy of the gum was due to the denture Greenbaum (UCutRev 1933 p. 841) reported 2 cases, 1 of which disappeared after oral hygiene w undertaken and the artificial dentures were adjusted; the dentures, h stated, did not touch the lesions. The case of Wachtle (DZtschr 69: 318 1934) was the sixth reported. Klugery a d Illge (JLancet 56: 495 1936) recorded 3 cases and reviewed 7 Of these 10 8 of which were in women, the ages of the patients ranged from 38 to 72 years. They thought that the vascular changes were important pathologic features. An ill-fitting upper plate pparently was etiologic in the case of Coomber (ADS 43: 1070 1941) Simmons (BMJ 1: 119 1941) reported cases as "prosthetic ulcers Penicillin troches were claimed to have been cura tive in a case of Hopper and Rogin (ADS 62 715 1950) but I have not been able t influence the disease with antibiotics locally o internally

Granuloma Pyogenicum (q v) may affect any part of the mouth. Dental granulomas and many epulides are really granuloma pyogenicum. The lesions are generally soft, deep red, easy to bleed, and pedunculated. Arising from the gingiva, a pyogenic granuloma is practically invariably associated with granuloma of the root of the tooth underlying Chronic ulcer of the mouth or tongue is similar to a granuloma pyogenicum of a sort which has not built up a papilloma but which extends through the depth of the mucosa and must be destroyed in its entirety before healing can take place The usual locations are the exposed surface of the lower lip the tip of the tongue, the cheek at the site of an accidental bite the gum overlying an infected dental root the dorsum of the tongue and the lingual tonsil

Treatment entails destruction, and any tooth that is involved must be sacrificed The lesions are not radiosensitive. The actual cautery or fulguration is best, and the base must be destroyed completely

Pyostomatitis Vegetans was the title under which McCarthy (ADS 60 716 1949) reported 3 cases in which stomatitis began with mi ute, flat miliary abscesses of lf ro size tendi g to conglomerate, located from to 3 mm. apart, with bases slightly raised, dark red and inflammatory The process spread d ri g period of a f w weeks to in vol e the whole mouth, the mucosa of which became prolif rative soft red folded a d verrucous. The abscesses pro ed persistent, and thei rupture resulted i rosion and exudate which could be peeled off particularly i the morning Smears from the abscesses showed polymorphonuclears, a proportion f them as great as 30% being eosinophils Symptoms were mild, the lesion n t tender, d the course benign and unusually chronic, showing ly slight variation of i tensity In 2 of the 3 cases, th lesions remained localized in the mouth, but in 1 there were bodil lesions resembling pyoderma vegetans. Local treatment was of no avail. Some be efit wa obtained with rest, l ver and iron. The cause was undetermined and no para ite was found which could be incriminated a pathogenic. If I see such a case I expect to try cortisone s if the patient had pemphigus.

Aphthae (Canker Sores) —These lesions are acute, painful, circumscribed ulcers which may be recurrent and which occur transiently either singly or in small numbers. The first stage is a tiny vesicle which enlarges a little and becomes eroded. The resulting soft painful flat, shallow ulcer is rarely wider than a few millimeters. Its floor is grayish white and fibrinous, and its narrow areola is brightly inflamed. Fetor is not a notable feature as it is in Vincent s disease, which differs also in being accompanied by salivation, fever and painful lymphadenopathy

The canker sore is exquisitely *tender*. Its location is generally on the inner surface of the lip beneath the tongue sometimes on the palate or uvula, occasionally on the gum. Coalescence of adjacent lesions may occur. The duration of a lesion from its inception to its spontaneous healing is likely to be about a fortnight. No scar ordinarily results.

The cause is not known. The lesions may represent stomatitis venenata (q v) in some cases, and are alleged to represent food allergy in many instances (Alvarez MinnM 20 602, 1937). Various foods are definitely provocative in certain individuals, especially chocolate nuts and sometimes fruits, but elimination dieting by trial and error serves to determine these not allergy tests (Rowe Elimination Diets and the Patient's Allergies, Lea & Febiger 1944). The herpes virus could not be demonstrated in recurrent aphthous stomatitis by Blank et al. (J 142 125 1950) or Stark et al. (JLab ClinM 44 251 1954).

TREATMENT.—The lesions may be touched with silver nitrate, which generally stops pain and apparently is followed by healing or compound tincture of benzoin may be used (Perlman ADS 61 119 1950). Brushing the teeth with soap was recommended by Fried (MünchMWchn 82 706 1935). *Fowler's* solution, diluted 3 drops to the ounce of water for a mouthwash was thought helpful by Becker (J 141 1272 1949). Histamine desensitization was tried by Porch (JLabClinM 26 499 1940). Vitamin therapy giving especially the *B* complex, has been highly recommended (Toone and Berkley VaM Month 66 282, 1939) or brewer's yeast (Hite VaMMonth 66 335 1939). Aureomycin in small dosage internally or applied in an ointment vehicle may appear to be curative (Nichamin J 141 1272, 1949 Gottlieb: abs J 148 1065 1952). While repetitious injections of smallpox vaccine have been tried as in the treatment of recurrent herpes (q v) this fails in treating aphthae (Kutscher et al. ADS 68 212 1953).

Periadenitis Mucosa Necrotica Recurrens (Recurring, Painful, Scarring Aphthae).—A lesion commences as a small inflammatory nodule beneath the mucous membrane of the lip cheek, tongue or throat. It gradually increases in size. After a few days sloughing occurs, and a solid, mummified-looking plug separates, leaving a crateriform depression. Pain is extreme. The lesions heal in a week or two leaving soft, grayish scars. They are usually single but 2 or 3 may be present at one time. Recurrence is the rule and the course extends over a period of years. Some patients have sores in various stages of their evolution more or less continually for years.

The mucous surfaces of the cheeks and lips are affected with about the same degree of frequency. The sides and undersurface of the tongue are attacked more often than the dorsum. The lesions are usually single but 2 or 3 may be present at one time. The ulcers are quite painful and so sensitive to irritation that the patients are likely to dispense with eating for many hours at a time.

Chronic aphthae of this type (Ulcus neuroticum mucosae oris, or Mikulicz's aphthae) were described by Sibley (BMJ 1 900 1899), who thought them "neurotic" in origin, and he quoted Jacobi (1894) as having reported 3 cases and reviewed others. Court (BMJ 1 1214 1899) wrote of a woman whose lesions were painful, pea to sixpence size ulcers which lasted for from 3 to 6 weeks and recurred over a period of 10 years or so. Lelbowitz (JCutD 29 [illegible] (AfDuS 10?: 191 1910) reported examples of this disorder and Sutton (JCutD [illegible] 1911) independently investigated and described a case and gave it the name I use. In the discussion of Epstein's case Jadassohn (ADS 1: 674 1930) said that it resembled a condition known on the Continent as "aphthae rebelles" he recommended prolonged arsenical medication. Morrow and Miller said they considered the disorder not excessively rare on the Pacific coast, and recalled 3 instances in which 2 or more members in a family had been attacked. In 1 of 2 cases of Davies (BJD 51: 177, 1939) the lesions appeared to migrate; he spoke of the disorder as "wandering ulcer". He, like myself, had no high regard for neurotic hypotheses. Neurotrophic ulcers, such as Mead (Diseases of the Mouth, Mosby 1933, p. 507) described were quite different lesions; they were probably pressure sores resulting from dental manipulations while the region was anesthetic.

The cause of the disorder is unknown. Leibowitz stated that ulcers occurred in the mouth after puberty and disappeared when the patient reached some 30 years of age but in Sutton's original patient the disease had been present since infancy. Secondary infec-

tion with Vincent's organisms and other bacteria frequently occurs. Fordyce (ADS 2: 253 1920) in discussing Fox's patient mentioned several that he had seen, among them a young woman in whom both the mouth and vulva were affected. He suggested that the lesions may be analogous to papulonecrotic tuberculids.

Histologically, intense inflammation is found in the periglandular tissues, with ensuing necrosis and the separation of the central portion of the affected area.

Treatment has been extremely disappointing *X ray therapy appeared* helpful in a case of Fergusson (BJD 51 325 1939) Repeated injections of smallpox vaccine appeared to account for 6 months of freedom from lesions experienced by a patient of Ronchese (ADS 56 653 1947) A dozen injections at intervals of 2 weeks was reported beneficial in 2 patients so treated by Grace (ADS 48 151 1943) My report (J 117 175 1941) of benefit with





Fig. 1950.—Periadenitis mucosa necrotica recurrens, involving buccal surface of upper lip. (Hayes Clinical Diagnosis of Diseases of the Mouth, Dental Items of Interest Publishing Co Inc.)

Fig. 1951.—Recurrent scarring aphthae, involving tongue.





Fig. 1952.—Periadenitis mucosa necrotica recurrens, showing the ulcer after separation of the slough. A smaller but similar lesion is present on the left side.

Fig. 1953.—Periadenitis mucosa necrotica recurrens involving the glans penis. (Dr H. J Templeton.)

sulfathiazole in 2 of 3 cases was premature for the drug helped no other patient of mine since that time. Aureomycin, used in 25% concentration as a mouthwash, helped 9 of 12 cases of Gottlieb (UgeskLaeger 113 1540 1951) Since 1952, I have found cortisone palliative and have corresponded with several physicians who have confirmed this; given by mouth in a dose of 25 mg., accompanied by KCl 5 gr Enseals, b.i.d. or t.i.d., it will keep the lesions in abeyance

See Michelson (ADS 8 842, 1923) case; Felt (ADS 31: 897 1935) case; Lordick (DMedWchr 1935, p 1804) cases Peck (ADS 41 1183, 1940) case with lesions also in axillae and groins; Graham (ADS 55: 709, 1947) case; Becerar et al. (ADS 58 842, 1948) case.

Cyclic Buccal Ulceration.—The lesions, recurrent periodically menstrual cycles, generally appearing several days prior to mens

are scattered and relatively painless, heal without scar and occur sometimes on the genital mucosae as well as oral The patients are of course females and they generally remain free of lesions during pregnancy but relapse subsequently Response to estrogenic therapy usually succeeds but is only palliative and must be persisted with (Jones: JObGyn 47 507 1940 Moseley JClinEndocrin 1 310 1941) Of the 8 cases reported by Pappworth (BMJ 1 371 1941) 6 were close relatives Chorionic gonad trophin, as well as estrogenic substances may relieve (Q&A: BMJ 1 205 1947) X ray therapy directed at the pituitary gland apparently cured the patient of Ziserman (JIM 8 6 193)

Black Tongue (Hairy Tongue Lingua nigra) —This peculiar and striking disorder was first accurately described by Rayer (Traite des Maladies de la Peau 1879) It has been comparatively rare only some 50 true cases having been recorded by 1910 (Heldingsfeld J A 2117 1910) The malady is characterized by yellowish brownish blackish or bluish discoloration of the affected area usually with accompanying papillary hypertrophy of variable degree Papillary overgrowth results in the formation of long slender hair like filiform projections which present an appearance comparable with that





Fig 1934 —Black hairy tongue
Fig 1935—Filament from black hairy tongue (Dr Fred Weidman)

of a windblown field of grain Various parts of the dorsum of the tongue may be attacked usually the central area lying immediately anterior to the circumvallate papillae

The malady may develop quickly or slowly The duration is variable The patient on discovering the condition is generally alarmed and he sometimes complains of a bad taste in the mouth or is able to feel the condition which disgusts him although other symptoms are usually absent.

The dirty coated or furred tongue is to be distinguished from black hairy tongue The former is related to transient variations in productivity and cohesiveness of normal epithelium It used to be taken with seriousness in estimations of health and prognosis, but the practice is obsolete No relation could be found between the state of the tongue in this regard and the state of the tonsils teeth nasal passages, lymph nodes of the neck, appetite or bowel action, by Gans (BMJ 2 1146 1934)

ETIOLOGY —Heidingsfeld was convinced that a parasitic cause could not be established I think inflamed, acanthotic and elongated filiform papillae become dark by oxidation, as comedones do Kennedy and Howles (ADS 4 1 566 1940) thought monilia to be etiologically concerned. The essential change is keratinization of the tips of greatly hypertrophic papillae according to Laskari and Corti (JID 13: 99 1949) who found various microorganisms but doubted the pathogenicity of them.

A gonorrheic patient given sulfanilamide developed black tongue and this disappeared when the drug was discontinued Bergheim (1939) told me. The relation of

penicillin therapy was observed soon after the antibiotic began to be used; 4 cases were reported by Wolfson (J 140 1206, 1949), and oral penicillin was recognized as the precipitating f ctor by Shaw (J 141: 143, 1949) The tablet nd lozenges have caused many cases (Ayre et al.: J 141: 848 1949; Overman: J 141: 1319 1949; Lefkovits and Lapidus J 143: 1483, 1950) Bl ck tongue f llowed the application of Aureomycin ointment on the lips (Bonchess and Kern: ADS 67: 503 1953) It developed in 10% of the patients treated with chloramphenicol and Aureomycin, generally aft r a week of therapy, reported Tomaszewski (BMJ 1: 1349 1953) and appeared following the application by him of Terramycin to the tongues of 2 of 4 volunteers. The disorder is a manifestation of stomatitis venenata wherein the papillae re hyperkeratotic, associated, perhaps, with tritional imbalance.

Hairy black tongue is harmless. Potassium chlorate, 0.3 Gm. t.i.d., cured a patient of Tomb (JTropM 43 155, 1940) Skillfully applied, an escharotic such as trichloracetic acid (Wise: ADS 32 291 1935) or 15% salicylic acid in glycerol (Marshall AnnOtol 49 961 1940) peels off the abnormal keratin. No local treatment is necessary if all possible causes of stomatitis venenata are prevented and if the patient is reassured, well nourished, and perhaps given generous doses of the vitamin B complex.

RED TONGUE.—A singular case was reported by Alvarez (J 87 1358 1926) due to a nonpathogenic, red, yeastlike organism.





Fig. 1956.—Geographic tongue. (Fox PaMJ 38 495, 1935.)
Fig. 1957.—Geographic tongue. (Dr George M. Mac Kee.)

Geographic Tongue (Transitory Benign Plaques of the Tongue).—Also known as erythema migrans, pityriasis linguae, glossitis areata exfoliativa exfoliatio areata linguae and wandering rash this disorder is characterized by almost asymptomatic, superficial, circinate, migratory inflammatory lesions which pursue an acute course disappear leaving no trace and recur at irregular intervals. The affection is fairly common. The eruption is usually confined to the sides and dorsum of the tongue It consists of one or more small, sharply defined, grayish, arcuate lines which spread peripherally with superficial exfoliation of the involved mucous membrane. The central region within the arc is beefy red in color and the margin is grayish or yellowish. After attaining a diameter of about 1 cm., the lesions tend to clear and they ultimately disappear Concentric rings may be formed. Two or more patches may coalesce giving rise to the polycyclic figures which constitute the condition known as geographic tongue The duration of an individual lesion is short from 2 to ~ days. Slight soreness may be present but as a rule symptoms are absent

ETIOLOGY.—The cause is unknown (Greenbaum ADS 39 686 1939) Its common conjunction with bad oral hygiene and infected teeth makes one believe that it must be correlated with the flora of the mouth. Prinz and Greenbaum (Diseases of the Mouth and Their Treatment, Lea & Febiger 1939 p 409) stated that it is a local expression of a constitutional neuropathic

anomaly," a view I think worthy of direct quotation for it paralleled neatly although it did not clarify the then current state of knowledge of this topic—upon which 16 years subsequently I can make no real improvement—in that it was dignified, sonorous, recondite and unintelligible.

Histology.—Larrot (ProgrèsMéd 1881, p. 191) found acanthosis and parakeratosis with edema of the rete and perivascular and cellular infiltration of lymphoid cells in the papillary and subpapillary layers of the dermis.

Diagnosis.—Leukoplakia, the mucous patches of secondary syphilis, and the more widely distributed symptoms of erythema multiforme and of pemphigus are readily distinguished.

Treatment.—The disorder is a persistent one, prone to relapse and recur. Regulation of the diet has been recommended. No specific remedy is known. The teeth should be cleaned and kept clean. The mouth must not be irritated by therapeutic efforts, for the disease itself is asymptomatic and innocuous. I do not try otherwise to treat these patients, who require only reassurance. Treatment usually proves futile or irritating, although Shaw (AIDS 56, 110, 1947) reported relief with a penicillin mouthwash, 1,000 units per cc. in saline. There is no reference to the condition in the Quarterly Cumulative Index in recent years.

Chronic Superficial Excoriation of the Tongue (Moeller's Glossitis) is a painful, chronic inflammatory disorder of the tongue affecting particularly the sides and tip, characterized by irregular, usually sharply defined, intensely red, soft, macular, erosive lesions in which the papillae appear thin and swollen.

The original description of Moeller (DeutschKlin 3: 273, 1851), translated by Rattner (AIDS 35: 463, 1937), described "... irregular, usually sharply defined, vivid red spots from which the epithelium is missing, or has become thinned. The papillae appear hyperemic and swollen and are elevated above the level of the normal mucous membrane. The areas are not covered with a pathological discharge; they are not transformed into ulcerations, nor do they have a tendency to spread. They are persistent, retaining their original size and form in spite of all forms of treatment. The lesions occur usually on the tip and margins of the tongue and sometimes the under surface and inside of the lips. The excoriations cause a very annoying burning sensation, giving a distaste for even the mildest food, although the appetite does not suffer. The sense of taste is dulled and sometimes the vertical movements of the tongue cause pain."

Some patients complain of severe and persistent burning and in others there are paroxysmal attacks of lancinating pain. The ingestion of acids and highly spiced foods generally provokes extreme discomfort. The disease is not rare. Harris (JCutD 33, 742, 1915) stated in his careful review with the report of 2 cases, but it is a hard one to relieve.

Diagnosis.—It is an entity quite readily confused with a variety of conditions. Cases called Moeller's glossitis fall into 5 classes: stomatitis venenata, stomatitis due to systemic allergy as in drug eruptions, stomatitis due to nutritional deficiency, glossodynia due to neural disturbance and, finally, true Moeller's glossitis, of which the cause is not known. In macrocytic anemia the tongue may become beefy red, smooth and painful, the process usually commencing at the margins. This may be an early symptom. Rattner pointed out that the symptoms of Moeller's glossitis are variable and may disappear for weeks or months. Sometimes itching rather than burning is the complaint, or mere discomfort. The pain may radiate to the ear or extend into the throat and esophagus, but is ordinarily confined to the patches of glossitis on the tip and lateral margins. Papillae within the patches are often hyperemic, swollen and elevated. When the tongue is extended, one may see whitish, longitudinal streaks on the dorsum near the base, and these change their apparent direction when the tongue is moved from side to side, being perhaps due to increased pressure from subsurface inflammation.

Treatment in the past has been disappointing. The young woman Rattner reported was asymptomatic during each of 2 pregnancies. Estrogenic substances do I have found relieve the condition and I obtained palliation in 2 patients with cortisone too, while it was being given. Desoxycorticosterone

acetate 10 mg per day yielded prompt improvement in a young woman with asthenia, low blood pressure amenorrhea and shallow ulcers of the tongue, when response to liver extract and vitamins had previously done little good reported Locket (BMJ 2 417 1945) The disease is not responsive to iron or vitamins, although these are certainly indicated and helpful in some cases of Hunter's glossitis and burning tongue (q v) One wonders whether hypoproteinemia (q v) may appertain.

Burning Tongue (Glossodynia)—Engman (ADS 1 137 1920) studied 11 cases of this clinically distinctive complaint. The patients are generally of middle age or older and the majority of them are women. The tongue gives rise to exceedingly distressing symptoms, described as burning or as if it had been scalded.' The front half of the tongue is the location of the sensation, and the sides are generally mainly affected. Rarely the symptoms are unilateral and sometimes the side of the cheek or of the lip may be affected too There is no visible alteration of the mucosa. The symptoms are continuous and severely annoying and may continue without change whether treated or not, over a period of years. Among the diseases that a dermatologist meets, it is one of the least responsive to treatment

The cause is not known. The condition was considered to be a symptom rather than an entity by Fox (NYSJM 35 881 1935) superficial glossitis with lingual symptoms justifying complaint may be due to galvanic lesions, stomatitis venenata, pellagra pernicious anemia, hypochrome anemia and avitaminosis. I believe rather that these various diseases are what they are and that glossodynia is something different. Lacking concrete factors on which to base an opinion of etiology some authors have guessed that the disease is primarily a psychoneurotic one, an *idée fixe* I doubt the truth of this hypothesis.

Lingual tonsillitis (q v) is a cause of abnormal sensations in the tongue, but it is not a cause of true burning tongue. Amyloidosis (q v) is a cause of enduring and incurable lingual distress. In Moeller's glossitis (q.v) objective evidence of glossitis is present, so that confusion cannot arise. Buccal neuralgia may be the equivalent of migraine in some instances or of tic douloureux of the ninth nerve in others (Hoover and Poppen J 107 1015 1936 Reichert: ASurg 41: 478, 1940)

In treating glossodynia, all sources of local irritation should be removed. The failure of local therapy was profound in the experience of Gilpin (J 106: 1722, 1936) Of his 48 cases, he stated that only a third were curable, and that arteriosclerosis of the brain was a common accompaniment of the disease. The investigation of nutritional and endocrine deficiencies must be undertaken, and suitable steps must be made to correct them if they are present. Tobacco does no good and perhaps does harm. All medicinal agents, particularly menthol and volatile oils, which might conceivably underlie stomatitis venenata must be prohibited. Roentgen therapy has been advised by some authors as a tentative measure sometimes yielding empirical aid. Cocainization of Meckel's sphenopalatine ganglion may be tried, or alcohol may be injected into it a measure recommended by Sluder (AmJMedSci 156 248, 1918) and approved by Prinz and Greenbaum (1939) Glossodynia leads to cancerophobia, and reassurance has some utility In a few unilateral cases, which I interpreted as segmental neuralgia (q v) and attributed to recurrent herpes without visible mucosal lesions, repeated intradermal injections of smallpox vaccine proved curative.

Costen's Syndrome.—Temporomandibular joint disturbances may provoke irritation of the auriculotemporal nerve and chorda tympani, as shown by Costen (ArchOtol 22: 554 1936) He reported 10 cases of lingual pain in which relief was obtained by adjusting joint function. When molars are ground low by attrition, or when prostheses are not high enough, the jaws may close so as to pinch the nerves and provoke unilateral pain in the tongue. Correction of the bite relieves the trouble.

See Bell (MJAustral 2 423, 1948) Ernenheiser (JOklaMA 33 284, 1930)

MALFORMATIONS AND BENIGN TUMORS

Mouth.—Clefts of various types, primarily of surgical interest, result from failures of embryologic development and fusion. Ichthyosiform nevi comprise one type of leukoplakia described with ichthyosis hystrix (q.v.). The oral ectodermal tissues, including the teeth, are defective in congenital ectodermal defect. In epidermolysis bullosa, mucosae may be abnormally vulnerable as is the skin (Forman, B.J.D. 8: 26, 1946).



Fig. 1938.—Nevus spongiosus albus mucosae, familial and congenital. No other mucosae were involved. (Cannon: Texas S.J.M. 41: 148, 1935.)





Fig. 1939.—Hemolymphangioma of tongue, causing macroglossia. (Dr. F. Ronchese.)
Fig. 1940.—Epidermolysis bullosa involving the tongue. (Dr. Norman Tobias.)

Cavernous or macular hemangioma may affect the mouth, often in accompaniment with extensive facial hemangioma. Cavernous lesions, with lymphangioma and hypertrophy, result in macrocheilia, macroglossia, macromelia and distortions and disproportions. Lymphangioma of the tongue in the case of Watrin et al. (Bsoefrancl) 46: 258, 1939) produced cysts, some of which were intraepithelial. Hereditary telangiectasia of Osler affects particularly the undersurface of the sides and tip of the tongue but also other parts of the

mouth; the little capillary ballooning, reddish purple soft, and multiple, may rupture and cause more or less severe hemorrhage V Recklinghausen's tumors, particularly neurinoma, affect the mouth (Martin and Graves J 117: 1535 1941) these firm, pinkish or whitish sessile or pedunculated, benign tumors are found about the lips and tongue.

Macromelia is hypertrophy of the cheek, macroglossia is hypertrophy of the tongue, and macrocheilia is hypertrophy of the lip These are sometimes congenital sometimes slowly progressive Macroglossia was due to muscular hypertrophy in one of the cases of VanMeter (KyMJ 40 273 1942) See Amyloidosis. In treating these lesions, plastic surgery is the only recourse

Lips.—Fordyce's disease, fistulas of the lips and capillary varices are described elsewhere.

Cheilitis Glandularis Apostematosa is a chronic disorder of the lips, characterized by swelling due to hypertrophy of the mucous glands and their ducts, with secondarily inflammatory symptoms of variable degree It was first described by Volkmann (AfpathAnat 1: 142, 1870) and possesses a considerable literature some of which is confusing The malformation is not





Fig. 1961.—Cheilitis glandularis apostematosa. (Sutton JCutD 27 140 1909.)
Fig. 1962.—Cheilitis glandularis postematosa: the pat lous mucous gland duct.

precancerous. When the lower lip is everted, one sees widely dilated sievelike openings, irregularly scattered over the vermilion border There is generally an associated hypertrophy of the mucous glands of the buccal and pharyngeal mucosa, and of the tissues of the turbinates and tonsils. When pressure is applied over the readily palpable glands, a glistening secretion exudes through the ducts and resembles drops of dew on the previously dried surface of the lip The patient often complains of the stickiness of the secretion but such complaint is generally due to psychiatric distress rather than the organic disorder (Woodburne and Philpott ADS 62 820 1950) Many of the glandular orifices admit the rounded end of an ordinary surgical probe The big mucous glands justify the name adenomatosis oris used by McCarthy and Shklar (ADS 70 293, 1954)

In a few of the reported instances, abscesses have developed, but this complication is unusual. It is particularly likely to occur if materials are rubbed onto the lip so as to introduce virulent organisms into hyperplastic but otherwise normal glands deep suppuration of the gland then ensues. Volkmann's original cases were suppurative Catarrh is common, due to the congenitally excessive supply of glandular tissue in the nose pharynx, mouth and lips. The malady was long supposed to be a rare one but cases must

have been overlooked or not recognized for mild forms are common, and even pronounced examples are not unusual. Puente (RevMédLat Am 20 937 1061, 1935) found it in 3% of his clinic patients. Touraine et al (BSocfrançD 42 539; 777 1935 43 687 1936) called the crusted cases "Volkmann's type," and the simple cases "Puente's type," of which the histologic structure showing simple glandular hypertrophy was determined by Sutton (JCutD 27:150, 1909 JMoMA 7 358 1911 InternatClin 3 24 1914).

The simple disease is persistent but benign and requires no treatment other than reassurance. The infected cases should be treated appropriately with antibiotics and dental care as indicated. See Waddington (BJD 65 466, 1953)

Gums.—Malformations here are particularly those associated with palatine clefts and with malformations of the teeth.

Hypertrophy of the Gums is a curious deformity which shows a hereditary tendency (Love BritJSurg 16 ... 1928). Its onset is early in life being sometimes congenital. Both jaws are affected as a rule. Involvement may be unilateral or bilateral. While the tissues look normal, they are so excessive in quantity that they cause gross deformity even actually covering the deciduous or permanent teeth giving rise to the so-called hippopotamus face (Hirschfeld JAmDentA 19 709 1932)



Fig. 1942.—Fibromatosis (congenital macrocheilia) in patient with hypertrichosis. (Drs. L. T. Byars and R. O. Sarnat, from Thoma Oral Pathology Mosby 1934)

This type of hypertrophy is distinct from that due to xanthomatous infiltration such as occurs in Gaucher's disease from neoplastic infiltration as leukemia and from hypertrophy associated with pregnancy (Monash: AJDS 24 580 1931) or irritation by dentures (Battaglia and Curpher AmJDis Child 57 1404 1939) or the gum changes caused by Dilantin (see Dermatitis medicamentosa). See James (Lancet 2 166 1919) primary hypertrophy case in girl. Matras (AfDuS 165 565 1932)

Swelling, bleeding, discharge and pain are absent. The tissues are firm, dense and fibrotic, the labial, lingual and occlusal aspects being equally affected. Mastication is hampered and the patient complains of deformity. Ruggles (J 84 20 1925) in an extensive review considered the lesion neoplastic, not merely hypertrophic, a kind of fibroma.

The structure has been described as almost keloidal, but in part it is made up of fibrous tissue with cells suggesting the structure of elephantiasis. The density of the fibrous tissue varies. Many large cells with pale protoplasm and deeply-staining nuclei are interposed. Some areas stain palely as though mucinous in nature (Hertzler Surgical Pathology of the Mouth and Jaws, Lippincott, 1938 p. 143)

No success in treatment may be expected except by surgical removal of the whole abnormal mass, including the teeth, alveolar process and soft tissues.

Palate.—Malformations of the palate include dysembryogenic clefts, angiomas which may bleed distressingly even though only a few millimeters in diameter exostoses and ecchondroses.

TORUS PALATINUS, the common midline bony lump or crest, is simply osseous excess at the line of union of the two halves of the palate It is asymptomatic unless bruised. It makes the fitting of upper plates difficult. It requires no treatment ordinarily but under some circumstances may need to be chiselled off. While some such protuberances are composed of bone, others consist mainly of cartilage and some areas within these may be myxoid (Hertzler 1938)

EPITHELIAL PEARLS of pinhead size are occasionally seen along the median palatine raphe in the newborn. These milia require no treatment.

Tongue.—Conspicuous congenital defects are rare. Tongue-tie or shortness of the frenum, is seen; usually it should be let alone, particularly in infants. Hypermobility has been recorded, as also have absence of the tongue, cleft tongue and microglossia. See Hemiatrophy (p. 1022)





FIG. 1944—Torus palatinus (Ivy Clinical Diagnosis of Diseases of the Mouth, Dental Items of Interest Publishing Company Inc 1935.)
FIG. 1945.—Scrotal tongue. (Dr Howard Fox)

Furrowed Tongue (Lingua plicata Grooved tongue Scrotal tongue) is a congenital malformation. Several members of a family may be affected (Tobias ADS 52 268 1945) The tongue is generally larger than normal and may be of extraordinary size (macroglossia) The grooves are plications of the mucous membrane, arranged usually with a deep longitudinal furrow running down the midline of the organ and shorter grooves coming off laterally like the veins of a leaf. In mild grades of deformity the wrinkles are superficial perhaps discovered only by accident. In pronounced examples of the disorder the deformity may be considerable so that particles of foreign matter lodge in the sulci. Excepting the possibility of its allowing the development of carcinoma to be obscured within a fold, the disorder seldom occasions consequential trouble (Berggreen DWchn 102 421 1936) See Lavenneville (La Langue Plicaturée, Paris, 1905)

A condition like grooved tongue may result from inflammatory hypertrophy and edema or from syphilitic scarring Neurosyphilis can cause atrophy of the musculature so that the mucosa undergoes plication. Aside from heredity syphilitic glossitis is the most frequent cause of furrowing of the tongue. Cerebriform nevus may affect one-half of the tongue furrowing it.

MAMMILLATED TONGUE refers to a heterogeneous collection of rare malformations (Weber BJD 57 179 1945) the name being purely descriptive

Retention Cysts of the Mucous Membrane involve the lips, the common location being in the inner aspect of the lower lip adjacent to the left cuspid (Sutton JCutD 36 579 1918) The lesions are somewhat paler than the normal mucosa because of their mucinous content and its expansile pressure. They are painless The content is a clear ropy fluid which escapes through any opening made in the cyst wall and recurs within the cyst as soon as the



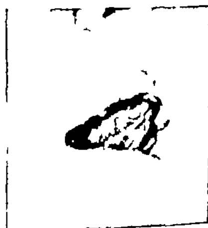


Fig 1946 —Mucous retention cyst [illegible] topped cyst under the mucosa of the lower lip
Fig 1947 —Mucocele of tongue (Thoma Oral Pathology Mosby 1934)





Fig 1948 —Branchial cyst (Dr R D Cattell, from Thoma Oral Pathology Mosby 1934)
Fig 1949 —Thyroglossal cyst (Dr R D Cattell from Thoma Oral Pathology Mosby 1934)

wound heals. Trauma surely plays a part in their causation for their onset sometimes may be dated to accidentally biting the lip They are perhaps due to dislocation of the duct or secretory tissue of a labial gland of Sebastian

Treatment entails destruction of the secretory epithelium which lines them. Mere incision does not suffice but Monash (ADS 25 1063 1932) found it successful merely to destroy the surface half of the cyst with endothermy so that the floor became continuous with the mucosa of the mouth; I have had less success with this method than he Following Pusey's suggestion, I have made a practice for years of removing retention cysts with the cautery One may puncture the dome insert a small forceps, pick up the base of the

cyst to invert it, pull forth the mass and dissect it off with the hot instrument. Another method that works satisfactorily is, after obtaining local anesthesia, to pick up the dome with an Allis clamp and excise with the cautery a disc of mucosa, pulling forth the glandular tissue attached underneath and removing the entirety of the abnormal gland. The wound is left gaping the patient is cautioned against eating things like popcorn, and the hole fills in painlessly and with trivial scarring after a couple of weeks. It is much easier to burn the tissues away than to dissect them with a scalpel.

Mucous Cysts may develop wherever mucous glands are found. They occur at any adult age (Hertzler) A cyst of the gland of Blandin Nuhn is one located beneath the tip of the tongue at the side of the midline. The size may be considerable

Ranulas are bluish cysts situated beneath the tongue, allegedly due to obstruction of the sublingual ducts, but if so they cause no disturbance of the gland (Hertzler) They may involve one or both sides of the midline The size may be so great as to interfere with phonation and eating and the tumor may project into the neck. Cohen and Kimmel (BMJ 2 87 1930) proposed to cure them, not surgically but by injecting into the cyst 2 cc. of 10% aqueous suspension of bismuth oxychloride followed by x ray therapy so as to obtain necrosis of the lining The result was, they said, a small nodular fibrotic scar





Fig. 1970.—Glossitis rhombica mediana. (Thoma Oral Pathology Mosby 1944)
Fig. 1971.—Glossitis rhombica mediana. (Alsehler ADS 30 400 1934)

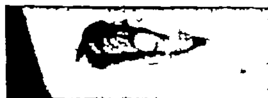


Fig 1972.—Neurilemmoma of the tongue, in young women. (Dr Sam E. Sweitzer)

Removal of a ranula requires more surgical skill than a dermatologist is likely to command.

Cholesteatoma may occur in the tongue as a midline tumor simply a wen in an unusual place. It can scarcely be distinguished from a midline fibroma or mucoid cyst until after incision or microscopic investigation (Hertzler) Such a lesion might be an implantation cyst (p. 1171)

Thyroglossal Cysts are cysts located in the midline of the tongue anterior to the epiglottis, due to dysgenesis of the thyroglossal duct. Interference with deglutition is a complaint. Until the tongue is drawn far out, the tumor is not seen. On palpation, it is found to be of walnut size smooth, spheroid and

elastic A sinus tract may connect it with structures in the neck by a passage through the hyoid bone The removal of such a lesion is no dermatologic undertaking Fistulas also occur (Kinsella BJS 26 714 1939)

Thyroid Tumors of the Tongue are interesting curiosities. The tumor is composed of thyroid glandular tissue located centrally at the base of the tongue at the foramen caecum. It is firm and elastic, small or large globoid, smooth or lobulated covered with mucosa and usually attached broadly It is functionally active as a rule perhaps containing islands of fetal tissue In 60 to 70% of the cases it constitutes all the thyroid tissue the individual possesses so that removal then results in myxedema (Ray Archsurg 7 316 1938) The condition is not extraordinarily rare for it comprises 1 out of 2 500 to 4 000 instances of all types of thyroid disease (Dietrich and Schall AnnOtol 61 ... 19 2) Radioactive iodine may be used to determine whether the tumor is functional and whether it contains a part or all of the thyroid tissue available to the patient (Nachman et al. J 140 1154 1949 Crispell and Larson SouthMJ 43: 945 1950 Sieber BMJ 2 186 1953 Zaslow et al J 165 359 1954) Malignancy has occurred in such lesions. Symptoms include dysphonia dysphagia, snoring pain cough discomfort a discommoding desire to swallow and, in 10 % of the cases hemorrhage

Treatment is surgical (Lemmon and Paschal AmJSurg 52 82, 1941)

Glossitis Rhombica Mediana is a rare asymptomatic lesion always located in the middle third of the dorsum of the tongue originally described by Brocq and Pautrier (AnndeD 5 1 1914 1915) The surface is smooth, shiny and reddish There is slight induration Usually the disorder is discovered by accident Nothing is known of its etiology and no treatment avails except excision or destruction.

Histologic changes are mesodermal the epidermis being normal. Sclerosis is found and this was interpreted, after study of 8 cases by Loos and Horbst (MOhrenNasenKehlk 138 122, 1934), to be representative of a vascular nevoid abnormality associated with the embryogenesis of the tuberculum impar The smooth bulge appears to be an excessive layer of subepidermal connective tissue The name I use for the condition was given by Lane (AJS J 548 1924) but it could be improved upon for the disorder is not inflammatory No treatment is necessary

See Arndt (Centralbl... 3 241 1922); Fordyce and Cannon (ADS 8 ... 1923) Zimmermann (DZtschr 44 163 19 8) Abahler (ADS 30 409 1934) Martin and Howe (AnnSurg 107: 39 1938) review

MALIGNANT LESIONS OF THE MOUTH

Neoplasms in the Mouth discussed elsewhere in this volume to which reference is recommended include: Cancer superficial, mucosal *Leukoplakia* Erythroplakia Bowen's disease Paget's disease Carcinoma of the mouth Melanoma Mixed tumor Myoblastoma Lymphoblastoma *Plasmoma*

Leukoplakia is whiteness of the mucous membranes, which normally look pink whiteness which exists because the avascular epidermal layer is abnormally thick for some reason or other This reason is sometimes neoplastic sometimes nonblastomatous see Welsh (Differential Diagnosis of Leukokeratosis and Cancer in the Mouth Thomas 1955) also p 1419

NEOPLASTIC LEUKOPLAKIA is the mucosal analogue of the cutaneous keratosis, and intergradient degrees of malignancy exist. See p 1165. *Leukoplakic* intraepidermal neoplasia and squamous intramesodermal carcinoma are distinguished only by time intervals and location of cancer cells. Neoplastic leukoplakia is superficial carcinoma (q v) Injuries may give its cells access into connective tissue When normal epithelium and abnormal epithelium grow side by side the normal under favorable circumstances, may supplant it replace it and re-cover the once abnormal area, so that the patch is gone for good, just as keratoses similarly may disappear One sees this particularly when the patient with chronic tobacco irritation and smokers patches gives up smoking and some—perhaps all—of his leukoplakic lesions peel off and

disappear within a few weeks. Those which remain after 2 months are dangerous and must be thoroughly destroyed. Neoplastic leukoplakia is irregular in outline but always is sharply marginated. The thicker it is, superficially set on the mucosa, the less instant is its danger in general. Thin, flaky easily bleeding leukoplakia, like the analogous keratosis senilis is dangerous erythroplakia simply requires time to do harm. The course of the histogenetic development of neoplastic leukoplakia into squamous carcinoma is analogous to the progress of the neoplastic keratosis into skin cancer With invasion of mesodermal tissues occur induration loss of flexibility fissuring and the development of palpable tumor Prompt metastasis is typical of ulcerative carcinoma of mucous membranes. Lesions which heap up in contrast with those which burrow in, are less malignant.

The individual who is prone to develop neoplastic leukoplakia and carcinoma of the mouth is the poorly pigmented male, possibly auburn haired who also is predisposed to develop actinic dermatitis and neoplastic keratoses. On the skins of these people it is the sun which immediately instigates the changes to which predisposition exists. In the mouth, it is generally the tarry distillate of tobacco which performs the same service. Saliva washes away much of the tar, but, where saliva dries along the external line of contiguity of the upper and lower lips, the tarry substance incites epithelial abnormality along more or less the whole extent of the lip The lower lip is affected principally for it is the one which is exposed to the sun

Treatment of neoplastic leukoplakia is, best, to destroy it with the actual cautery Destruction does not need to be deep but must be wide to include all the patch, missing no square millimeter of it. One intends that the replacement of new epithelium be derived from normal epithelial cells (see pp 1191 and 1227)

Carcinoma of the Mouth is discussed on pp 1205 1233 and 1234

Lymphoblastoma, especially monocytic (q v) commonly results in infiltration of the gums. Hypertrophy begins as a rule about the lower front teeth The papillae are greatly enlarged, the gingival tissues are soft and succulent salivation is profuse, and excoriation and infection of the gums lead to bleeding soreness and fetor Noma may terminate acute leukemia. See also Mycosis fungoides.

Sarcoma of the mouth may be primary see sarcoma of the tongue Tonsillar lesions sometimes develop so rapidly into fungating ulcerous masses with cervical node metastases, that one suspects infection instead of blastoma. Mycosis fungoides may manifest oral lesions. Kaposi s sarcoma often does. Osteosarcoma, antrum tumors, tumors of the jaws, adamantinomas, radicular cysts and dentigerous tumors are merely mentioned here. Fibroma, lipoma, myoblastoma, angioma and neurofibroma and plasmoma—each described elsewhere heretofore—may occur in the mouth. Melanoma of the palate was noted by Arons (Laryng 49 271 1939) chondroma of the tongue by John (JMichSMS 41 471 1942) primary lymphosarcoma of the palate by Freeman (AmJRoentg 43 702 1940)

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